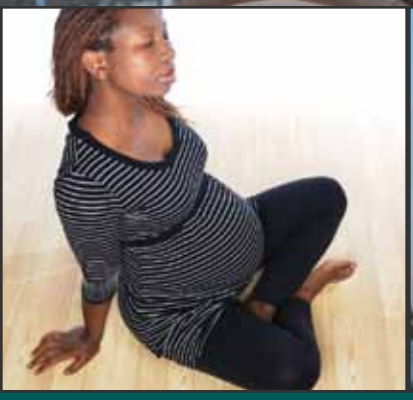


Early Exposures to Hazardous Chemicals/Pollution and Associations with Chronic Disease: *A Scoping Review*

June 2011

A Report from the Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada

This publication should be cited as follows:

Cooper K, Marshall L, Vanderlinden L, and Ursitti F (2011) *Early Exposures to Hazardous Chemicals/Pollution and Associations with Chronic Disease: A Scoping Review*. A report from the Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada.

Le résumé de ce document est également disponible en français au www.cela.ca et www.healthyenvironmentforkids.ca

ISBN 978-1-926602-87-5

CELA Publication #795

Printed in Canada on paper containing 100 per cent post-consumer recycled content.

Table of Contents

Foreword from CPCHE and OCDPA

In 2008, the Canadian Partnership for Children's Heath and Environment (CPCHE) and the Ontario Chronic Disease Prevention Alliance (OCDPA) – together comprising more than 35 organizations – embarked upon a multi-year collaboration, funded by the Ontario Trillium Foundation, to explore the known and suspected links between early environmental exposures and the later development of chronic disease. This collaboration was centred around the two networks' shared commitment to health promotion and a common concern about chronic diseases – specifically asthma, cancer, cardiovascular disease, diabetes and neurodegenerative disorders, among others – that are affecting large numbers of people. It was also based on a recognition that opportunities for prevention start early: during infancy and childhood, in the womb and even prior to conception.

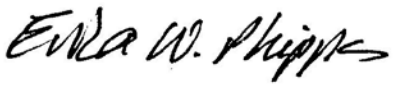
The burden of chronic disease in Ontario and across the country is very high. In Ontario, about one in three people (all ages) have one or more chronic diseases. At least 60 percent of Ontario's health-care costs are related to chronic disease. Within the multiple determinants of health, it is understood that chronic diseases are typically complex conditions with multiple risk factors some of which can be the result of lifelong influences and circumstances. The social determinants of health are increasingly understood to be of paramount importance in contributing to the most common chronic diseases and their better-understood biomedical and behavioural risk factors. Adding to this complexity is the potential influence on chronic disease of environmental exposures, such as air pollution and other toxic substances, including the need to consider key differences between effects in adulthood versus during childhood or in the womb.

We know that, compared to adults, children are more exposed to toxic substances in their environment because of differences in size, intake and behaviour. They are also more vulnerable to adverse effects of toxic exposures. The flip side of this early vulnerability is that exposure reduction efforts specifically targeted at these formative years could have positive implications for lifelong health, particularly when combined with ongoing efforts to promote healthy eating and exercise, combat poverty and address other determinants of health.

The CPCHE and OCDPA partners are pleased to welcome this report, which has been prepared by the Canadian Environmental Law Association (CELA) in collaboration with experts in medicine and public health as a substantive contribution to our ongoing CPCHE-OCDPA collaboration. Applying the multiple determinants of health framework, the report

places the evidence about environmental risks in the broader context of existing knowledge about the multiple risk factors for several common chronic diseases. As such, it provides the two networks and the broader community with an evidence base from which to explore opportunities for prevention-oriented improvement in policy and practice.

The mutual sharing of expertise and perspectives between the chronic disease prevention and children's environmental health protection sectors, via this project, have resulted in new collaborations and a deeper understanding of the intrinsic linkages between our respective mandates and efforts. Fundamentally, the mandates of both networks include the prevention of chronic disease with a precautionary approach underpinning our collective health promotion efforts. We look forward to using these newly established connections and enhanced knowledge as we continue to work towards a healthier Ontario.



Erica Phipps
CPCHE Partnership Director
on behalf of CPCHE

Norman Giesbrecht and Chris Markham
OCDPA co-chairs
on behalf of OCDPA

canadian partnership for children's health & environment
partenariat canadien pour la sante des enfants et l'environnement

OCDPA
Ontario Chronic Disease Prevention Alliance

Acknowledgements

The Canadian Partnership for Children's Health and Environment (CPCHE), the Ontario Chronic Disease Prevention Alliance (OCDPA), and the Ontario Public Health Association as the project lead, gratefully acknowledge the funding support of the Ontario Trillium Foundation for the Joint CPCHE-OCDPA Initiative on Early Environmental Exposures and Chronic Disease Prevention, within which this report was developed.

Thank you also to the following individuals for providing expert advice, technical information, assistance and/or comments on the overall project and the production of this report:

Salima Allibhai-Hussein, Canadian Cancer Society*

Mary Anderson, Canadian Environmental Law Association

Josephine Archbold, Toronto Public Health

Louise Aubin, Peel Public Health*

Myriam Beaulne, formerly with CPCHE

Samantha Burdett, formerly with the Ontario Trillium Foundation

Siu Mee Cheng, Ontario Public Health Association

Cathy Conway, Alzheimer's Society of Canada*

Robert Dales, University of Ottawa

Hoi Ki Ding, formerly with OCDPA

James Draper, Ontario College of Family Physicians*

Norman Giesbrecht, Centre for Addiction and Mental Health

Renee Griffin, Canadian Environmental Law Association

Karen Karagheusian, Canadian Cancer Society*

Bruce Lanphear, Simon Fraser University

Fe de Leon, Canadian Environmental Law Association

Mary Lewis, Heart and Stroke Foundation of Canada

Erin Hodge, Ontario Agency for Health Protection and Promotion

Randee Holmes, Canadian Partnership for Children's Health and Environment

Adele Iannantuono, Health Canada

Jan Kasperski, Ontario College of Family Physicians*

Jennifer Lodge, Ontario Public Health Association / OCDPA

Carole Madeley, Ontario Lung Association

Husam Mansour, Pollution Probe

Chris Markham, OPHEA

Matthew Mayer, Heart and Stroke Foundation of Canada

Lynn Marshall, Ontario College of Family Physicians and Environmental Health Institute of Canada

Wendy McAllister, Health Nexus*

Theresa McClenaghan, Canadian Environmental Law Association

Robb MacDonald, MacComm Social Marketing

Barbara McElgunn, Learning Disabilities Association of Canada

Jacquie Micaleff, Alzheimer's Society of Canada*

Erica Phipps, Partnership Director, Canadian Partnership for Children's Health and Environment*

Glenn Pothier, GLPi

Shadab Rana, Heart and Stroke Foundation of Canada

Maja Saletto Jankovic, Ontario Trillium Foundation

Shawna Scale, formerly with OCDPA

Meg Sears

Barbara Snelgrove, Parkinson Society Canada

Linda Stewart, Association of Local Public Health Agencies (former co-chair of OCDPA)

Brian Stocks, formerly with Ontario Lung Association*

Sue Turner, Heart and Stroke Foundation of Canada*

Connie Uetrecht, formerly with Ontario Public Health Association*

Franca Ursitti, Ontario Public Health Association and Peel Public Health*

Loren Vanderlinden, Toronto Public Health*

Connie Wong, Ontario Lung Association*

Thanks especially to the members of the Project Steering Committee, past and present, denoted with an asterisk in the above list, and all those who participated in stakeholder events held during the project.

This report was researched and written by **Kathleen Cooper**, Senior Researcher with the Canadian Environmental Law Association with the assistance of **Dr. Lynn Marshall**, President of the Environmental Health Institute of Canada and Alternate Chair, Environmental Health Committee, Ontario College of Family Physicians, **Dr. Loren Vanderlinden** and **Franca Ursitti**. The report content is the responsibility of the authors and not their institutions unless otherwise specified. Grateful acknowledgement is also extended to **Erica Phipps**, CPCHE's Partnership Director for managing this initiative.

Layout and production was done by Chris McKinnon**.**

Disclaimer: Inclusion of the names and affiliations of individuals or groups is for acknowledgement purposes only and should not be taken to constitute an endorsement. The Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada are solely responsible for the content of this publication.

List of Acronyms and Abbreviations

AAP – Amyloid Precursor Protein
AD – Alzheimer's Disease
AHA – American Heart Association
ALL – Acute Lymphocytic Leukemia
AML – Acute Myeloid Leukemia
BCF – Breast Cancer Fund
BPA – Bisphenol A
BFRs – Brominated Flame Retardants
CACs – Criteria Air Contaminants
CELA – Canadian Environmental Law Association
CPCHE – Canadian Partnership for Children's Health and Environment
CMA – Canadian Medical Association
CO – Carbon Monoxide
COPD – Chronic Obstructive Pulmonary Disease
CTUMS – Canadian Tobacco Use Monitoring Study
CVD – Cardiovascular Disease
DES – Diethylstilbesterol
DNA – deoxyribonucleic acid
DOHaD – Developmental Origins of Health and Disease
EAF – Environmentally Attributable Fraction
ECD – Early Child Development
EDCs – Endocrine Disrupting Compounds
ETS – Environmental Tobacco Smoke
EU – European Union
HPA axis – Hypothalamic-Pituitary-Adrenal axis
IARC – International Agency for Research on Cancer
IgE – Immunoglobulin E
ICAP – Illness Costs of Air Pollution
LBW – Low Birth Weight
MDOH – Multiple Determinants of Health
NHANES – National Health and Nutrition Examination Survey (United States)
NHL – Non-Hodgkin's Lymphoma
OC pesticides – Organochlorine Pesticides
OCDPA – Ontario Chronic Disease Prevention Alliance
OCFP – Ontario College of Family Physicians
OMA – Ontario Medical Association
OP pesticides – Organophosphate pesticides
PAHs – Polyaromatic Hydrocarbons
PBDEs – Polybrominated Diphenyl Ethers
PCBs – Polychlorinated Biphenyls
PD – Parkinson's Disease
PFOA – Perfluorooctanoic Acid
PFOS – Perfluorooctane Sulfonate
PM – Particulate Matter
PVC – Polyvinyl Chloride
POPs – Persistent Organic Pollutants
ROS – Reactive Oxygen Species
SDOH – Social Determinants of Health
T-cells – thymus-cells
TGCC – Testicular Germ Cell Cancer
VOCs – Volatile Organic Compounds
WHO – World Health Organization

Executive Summary

Project Scope and Report Overview

This report is a product of a network to network collaboration among groups involved with the Canadian Partnership for Children's Health and Environment and the Ontario Chronic Disease Prevention Alliance (CPCHE and OCDPA) to provide a baseline for further collaboration. The central focus is a scoping review of evidence for associations between early life environmental exposures and the later development of several of the most common chronic diseases.

Part One provides context about chronic disease and care in Canada's aging population, the reality of the multiple determinants of health, the primacy of the social determinants of health, the considerable breadth of environmental influences on health, the importance or early child development to lifelong health and the scope and complexity of multiple inter-relationships among all these health determinants.

Part Two introduces the Developmental Origins of Health and Disease (DOHaD) concept and the related and expanding field of epigenetics. It also discusses key issues that arise in evaluating evidence in complex environmental health issues. The main focus is review of the multiple risk factors for several common chronic diseases (cardiovascular disease, type 2 diabetes, several cancers, asthma, Alzheimer's disease and Parkinson's disease) and includes a detailed look at the evidence for links to environmental exposures. Evidence is reviewed for associations between health outcomes and both adult exposures and early life exposures, including in the womb.

Main Findings

Overall conclusions include the fact that chronic diseases and interrelated contributory factors are far more complex than is implied in, or amenable to response strategies focused solely on individual behavioural changes. In particular, there is a critical need to address poverty and the social determinants of health (SDOH) given the reality of biomedical and behavioural risk factors for various diseases arising from social and economic conditions. Environmental influences on health are multifaceted, involving multiple pollutants, exposure routes, on a scale ranging from macro to micro (e.g., from built environment features to the loading of floor dust with toxic substances), multiple interrelationships, and life course vulnerabilities. It is already well-established that the *in utero* and perinatal "environment" and maternal and early childhood circumstances play major roles in the risk of later life disease. Within this new paradigm for disease causation, the DOHaD concept and the related field of epigenetics, a rapidly expanding body of research indicates a role for early life exposure to environmental contaminants in this lifelong continuum of disease vulnerability. Because of the abundant complexity, not only is there a need for more research, but also to adjust assessments of the strenghth of evidence for associations between risk factors and health outcomes via tools such as the Bradford Hill criteria and hierarchical models of study designs. Given the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures, a broader approach to prevention is worthwhile. The following table provides a summary of early exposures (*in utero* or childhood) for which there is evidence of associations with prevalent chronic diseases addressed in this review.

Chronic Disease and Care in Canada's Aging Population

Canada has an aging population (currently 13% are aged 65 and over, predicted to rise to 25% by 2036) with high prevalence and in many cases rising incidence of many chronic diseases. 80% of those over 65 have one chronic disease, and, of those, 70% have two or more chronic diseases. More and more children are experiencing chronic diseases, or conditions that lead to chronic diseases. Low birth weight and preterm births are understood to be indicators of potential lifelong consequences (as discussed throughout this report) and incidence of preterm birth in Canada (excluding data from Ontario) has been rising steadily for 20 years.

Table 1: Summary of Early Exposures Associated with Prevalent Chronic Diseases or Conditions

NOTE: Important detail about strength of evidence is lost with this aggregation – see specific sections of this report for more detail	
Cardiovascular disease (CVD)	• Lead, smoking, particulate air pollution, • Substances associated with cardiac birth defects • Substances associated with low birth weight • Endocrine disrupting substances affecting insulin signalling (BPA and phthalates), adult dev'mt of polycystic ovarian syndrome (BPA and other EDCs), lower testosterone levels in adults (BPA, phthalates, PCBs), and dysfunction in HPA-axis and stress response (lead).
Cardiac Birth Defects	• Ambient air pollution (specifically carbon monoxide and ozone), organic solvents in dyes, lacquers and paints (specifically halogenated hydrocarbons including trichloroethylene and dichloroethylene), chlorophenoxy herbicides, trihalomethanes, additional pesticides, ionizing radiation, lead, benzene, sulphur dioxide, ETS.
Low Birth Weight	• Air pollution – CACs (particularly sulphur dioxide and particulates), maternal smoking, ETS, PAHs, lead, mercury, arsenic, OC and OP pesticides, nitrates in drinking water, phthalates, BFRs, polyfluorinated compounds.
Obesogens	• Endocrine disrupting substances suspected as obesogenic (BPA, phthalates, organotins, PBDEs, polyfluoroalkyl compounds, OC pesticides, PCBs) • Human adenovirus 36, phytoestrogens, glycyrrhetinic acid (sweetener)
Type 2 Diabetes	• Prudent to assume that known continuum of common risk factors across CVD, metabolic syndrome and diabetes likely extends to early environmental exposures • Substances associated with low birth weight • Endocrine disrupting substances relevant to CVD • Suspected obesogens
Alzheimer's disease	• Prudent to assume that known continuum of common risk factors across CVD, metabolic syndrome, diabetes and Alzheimer's disease likely extends to early environmental exposures • Air pollution, lead
Parkinson's Disease	• If link to obesity confirmed, prudent to consider obesogens as environmental risk factors • Air pollution, certain pesticides (maneb and paraquat, OC pesticides)
Developmental Neurotoxicity	• Lead, mercury, arsenic, manganese, organic solvents, OP and OC pesticides, PAHs, ETS, PCBs, phthalates, BPA, dibutyltin, PBDEs, triclosan, artificial food colours and additives.
Cancer • Breast • Prostate • Testicular • Other Cancers	• Breast cancer: ionizing radiation, benzene and organic solvents, 1.3-butadiene, aromatic amines, BPA, phthalates, parabens, alkylphenols, PAHs, OC and triazine pesticides, PBDEs and other POPs, metals, tobacco and ETS, vinyl chloride, ethylene oxide. (See also Table 6.) • Prostate cancer: Synthetic hormones in food production, BPA • Testicular cancer: Maternal exposure to several POPs • Testicular Dysgenesis Syndrome: EDCs with anti-androgenic action (phthalates, some pesticides, BPA) • Other Cancers: particulate air pollution, radon, multiple pesticides, chlorination byproducts, cadmium, aromatic amines, PAHs, diesel exhaust, smoking and ETS, dioxin, ionizing radiation, vinyl chloride, some paints and solvents, cell phone use (see also Table 5)
Respiratory disease (asthma)	• Substances associated with low birth weight • Smoking and ETS, aeroallergens, indoor and outdoor air pollution including all the CACs (ozone, CO, PM_{10} and $PM_{2.5}$, nitrogen dioxide, sulphur dioxide, many different VOCs), multiple hazardous air pollutants (PAHs, aldehydes, acide vapours and aerosols, diesel exhaust), formaldehyde, VOCs, phthalates, aldehydes, isocyanates, anhydrides, cadmium, hexavalent chromium, manganese, nickel, benzene, dibutyl phthalate, dioxins, PCBs, metals (esp. lead), some pesticides, BPA, perfluorinated compounds

In Ontario, one in three people (of all ages) have one or more chronic diseases, and at least 60% of Ontario's health care costs are due to chronic diseases. In Canada, the prevalence of the most prominent chronic diseases is estimated to be in the multi-millions of affected individuals. Cost estimates are in the multi-billions of dollars with indirect costs, particularly of family caregivers, generally unrecognized.

There is strong and consistent evidence of socio-economic disparities in health, with significantly poorer health and shorter life expectancy for those living in poverty. The annual disease burden attributable to environmental exposures has been estimated from studying mortality, hospitalizations, patient-days spent in hospital, low birth weight, and serious congenital anomalies, for four major categories of diseases (respiratory, cardiovascular, cancer, and congenital affliction). Annual costs in Canada are conservatively estimated to be between $3.6 and $9.1 billion.

Understanding Environmental Exposures

Environmental exposures can include chemicals used in myriad products or released to the environment as various forms of pollution. Toxicants can be present in air, soil, dust, food, water, and consumer products, as well as simultaneously across all media. The reality of multiple exposures occurring across multiple media and often changing over time and by location creates major challenges in understanding relationships between environmental exposures and health outcomes.

Criteria air contaminants (CACs) in outdoor air pollution include coarse, fine and ultra-fine particulate matter (PM), carbon monoxide, oxides of sulphur and nitrogen, ammonia and volatile organic compounds (VOCs). Levels of these pollutants are highest in areas of high traffic volume, industrial activity, coal-fired electricity generation, and residential wood fuel combustion. Smaller contributions arise from many other activities. Lower volume, diverse outdoor air pollutants that are frequently more toxic at lower exposure levels are emitted from similar sources. For example, the largest sources of dioxin and furan (highly toxic persistent organic pollutants – POPs) emissions in Canada are from the incineration of municipal and medical waste.

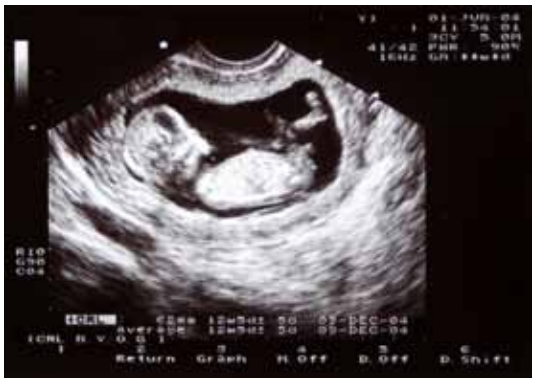
Soil pollution can result from legacy industrial site contamination or use of toxic metals (e.g. lead in paint and gasoline; arsenic as a wood preservative).

Indoor air pollution arises largely from consumer products, which are increasingly understood to partition into house dust, as well as products of combustion, biological allergens, and radon. Drinking water may contain disinfection byproducts, industrial effluents and pharmaceutical residues, biological contamination, as well as geological contaminants such as arsenic, or lead used in plumbing.

Food contamination depends on food type, processing, packaging, storage, and preparation methods, as well as fat content (lipophilic contaminants tend to be persistent and bioaccumulative, and are often highly toxic). A mother's body is a child's first environment, with many toxicants able to cross the placenta and to be expressed in breast milk.

Extensive evidence indicates that house dust contains more than 100 potentially toxic substances and allergens. House dust and PM in indoor air, from indoor and outdoor sources, are among the most important media for childhood exposures to lead, PBDEs, pesticides, polyaromatic hydrocarbons (PAHs), phthalates and other endocrine disrupting compounds (EDCs), arsenic, chromium, mould, endotoxin and bacteria.

Fetus and Child More Vulnerable



Infants and children are more exposed to environmental contaminants than adults because of their relatively larger absorptive surface areas, more rapid breathing, higher rate of ingestion, and hand to mouth exploratory behaviour. They are also more vulnerable to these exposures due to rapidly developing, still immature organs and body systems, including detoxification systems. Some children are genetically more susceptible to environmental insults, with lifelong implications.

Widespread Exposure of Uncertain Significance

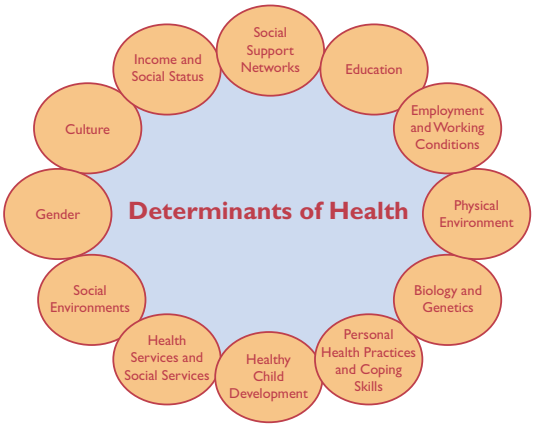
Human biomonitoring has revealed multiple chemicals in blood, urine, breast milk, and sometimes hair and nails, both in large population-based studies in Canada and the U.S., as well as in several smaller studies. Humans of all ages, from newborns to those entering their 8th decade, have retained legacy substances such as lead, mercury, PBDEs, PCBs, and organochlorine (OC) pesticides, as well as substances still being produced such as BPA, phthalates, perfluorinated compounds, acrylamide and perchlorate. The consequences of exposure to low levels of multiple substances are uncertain and the subject of extensive study.

The Multiple Determinants of Health

Many complex and dynamic factors combine, and often interact, to influence individual and population health. The Multiple Determinants of Health (MDOH) framework is useful but it can be limited in conveying the breadth of issues in the areas of social determinants of and environmental influences on health.

Application of the model in public health or health sciences focuses heavily on behavioural and biomedical risk factors, whereas quantitative and qualitative evidence from around the world points to crucial influences of the social determinants of health (SDOH) and early child development (ECD). There is also increasing evidence of the role environmental factors, such as exposure to pollution and toxic chemicals, play in the development and exacerbation of many chronic illnesses, but these have received limited attention in the SDOH and ECD literature.

Behavioural or modifiable risk factors include smoking and alcohol consumption, as well as exercise and eating habits, which commonly overlap with intermediate conditions known to be associated with chronic disease. Such intermediate conditions can include biomedical risk factors such as high blood pressure, high blood cholesterol, obesity, and high blood sugar. Chronic disease prevention strategies give priority to addressing the "big three" behavioural risk factors: unhealthy eating, physical inactivity and tobacco use/exposure. However, this focus belies the underlying importance of the SDOH, that is, the economic, social, and living conditions of daily life.



While behavioural choices or biomedical factors are individual, societal conditions are fundamentally influential. Although ill health is most prominent among the poorest of the poor, the World Health Organization confirms that health and illness follow a social gradient worldwide: at all levels of income, the lower the socioeconomic position, the worse is a person's health. In Canada, this gradient seems to disproportionately affect newcomers to Canada and Aboriginal communities. Inattention to the SDOH as primary determinants can undermine individual behavioural choices to achieve better health, including the ability to adopt such choices at all.

Environment is similar to income level or gender in being a cross-cutting determinant of health that interacts in many different ways with other determinants, especially the SDOH. Environmental determinants can encompass the entirety of indoor and outdoor circumstances of people's lives, with multiple media and routes of exposure that can vary widely according to activities occurring on a scale from individual to local to regional to global.

For example, some key issues are land use planning choices that result in a pervasively automobile-dependent lifestyle that in turn contributes to health-harming air pollution and climate change; a built environment that contributes to sedentary lifestyles and related overweight/obesity; and an increasingly mechanized, centralized and fossil fuel-dependent food production and marketing system that has altered the composition of food and is a major contributor to climate change and the glut of inexpensive sources of unhealthy food.

Many severe health impacts of climate change are expected to occur in coming decades when an unprecedented one quarter of the population will be over age 65 and, if current trends continue, the overwhelming majority if these seniors will be afflicted with at least one or more chronic diseases. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health- air, food, water and shelter.

Interacting Environmental and Social Risk Factors

There is evidence of more pronounced impacts of air pollution among poorer people, with higher pollution-related hospitalization and mortality rates. There is a greater likelihood that communities with low income and/or racial minorities to live near polluting industrial facilities, hazardous waste sites, or high traffic corridors. Poor quality housing can increase exposure to mould, other biological allergens, pesticides, lead, asbestos, and likely other contaminants. A 30-year retrospective analysis of population health and housing found that poor housing quality was related to higher levels of asthma, respiratory illness, obesity, diabetes, and lead poisoning, among other adverse health outcomes.

When nutrition is inadequate, children and the developing fetus are at greater risk from environmental exposures because deficiencies in protein, calcium or iron can enhance absorption of toxic substances such as lead. Cultural, as well as economic influences, affect intake of food-borne contaminants such as mercury and lipophillic POPs in fish; this occurs more often among Aboriginals, coastal community residents, and immigrant populations from Asia.

Combining both locational and nutrition issues, low income communities can also tend to have limited access to stores selling good quality food, greater access to fast food outlets, and an overall tendency to consume lower quality, energy dense foods due to greater affordability.

Smoking prevalence is twice as high among lowest income Canadians compared to the highest, but the Canadian Tobacco Use Monitoring Study shows a downward trend in most age groups, particularly in the percentage of children exposed at home to ETS.

Many early environmental exposures of concern originate in consumer products. These can include legacy components such as lead, PCBs, banned pesticides and flame retardants and newer components such as phthalates and BPA in plastics. These and many other contaminants are known to partition to house dust and can be at very high levels in older carpets. Such product-based indoor exposures are plausibly higher in the poor because of longer use of lower quality or second-hand goods, including older dust-laden carpets, and greater consumption of canned food affected by BPA-containing can liners. Exposure to lipophilic toxic substances will also be higher among those consuming a high fat diet.

Early Child Development

Early experiences fundamentally affect how the structure of the brain develops in early childhood, the evolution of emotional and social temperament and coping skills, abilities with language

and literacy, perception and cognition, and attitudes that may affect capacities for both physical activity and psychological health. Literature on early child development confirms a strong correlation between disadvantaged conditions in childhood and multiple aspects of poorer health later in life. There are long-term economic consequences of thwarted child development in terms of loss of human capital, poor health and insufficient community services.

There is a striking absence from the Canadian ECD literature of consideration of the developmental neurotoxicity of environmental contaminants. The fact that the otherwise exemplary and influential Canadian studies on this topic do not consider the evidence about the developmental neurotoxicity of environmental exposures, particularly the greater vulnerability *in utero*, illustrates a valuable reason for the collaboration behind this report; to review the evidence of environmental contributions to chronic diseases, and to put it into necessary context.

The Causal Puzzle

There is a tendency for research to be reductionist, focusing on multiple but separate environmental risk factors for chronic disease, i.e. individual pieces of the puzzle, rather than the causal puzzle itself. For example, understanding of the individual and combined effects of the domains of toxic substances, social environments, and nutrition is aided by recognition of how multiple factors can occur and interact within each domain as well as across two or all three, and that the relative importance of each can vary by circumstance. Understanding is hampered by large knowledge gaps about the health impacts and exposure circumstances of the many toxic substances to which children are exposed, as well as the potential for interactions.

The Developmental Origins of Health and Disease (DOHaD) and Epigenetics

The Developmental Origins of Health and Disease (DOHaD) explores the associations between adverse events during vulnerable, early life stages and later life patterns of health and disease, such as the relationship between maternal prenatal undernutrition, low birth weight and increased risks for metabolic syndrome, diabetes, cardiovascular disease, malignancies, osteoarthritis and dementia in adulthood.

Considerable evidence points to the *in utero* and perinatal environment as playing a major role in later life disease risk with epigenetic processes, or gene-environment interactions, as one important explanatory mechanism. “Environment” here is broadly defined to include maternal age, health status, nutrition, stress levels, etc. However, the similar concept of “windows of vulnerability” describes the greater vulnerability of the developing fetus or young child to environmental exposures during early life. Herein is a key nexus between the work of CPCHE and OCDPA.

Epigenetics processes likely underlie aspects of the toxicity of many environmental exposures of concern and are therefore highly relevant to understanding the evidence about early exposures to chemical substances and the development of chronic disease. The Bradford Hill criteria for causation provide useful signposts for judging the overall strength of an association and by extension, strength of a body of evidence. However, they are inadequate to the task of evaluating the complex and dynamic processes that contribute to disease in a multi-causal model.

Indeed, for environmental exposures that may fundamentally alter the life course via impacts on prenatal or perinatal development, a demand for epidemiological evidence to confirm the

existence of a chronic disease risk factor has significant implications. Application of the Bradford Hill criteria of analogy and plausibility could be more prudently applied to early environmental exposures in the context of recognizing that epidemiological evidence does not tend to become available until long after widespread exposure and often irreversible environmental contamination has occurred.

Early Exposures and Cardiovascular Disease

Despite a trend to dramatically decreasing rates of CVDs in Canada in past decades, the burden of CVD is expected to remain considerable, due to changing demographics and the prevalence of underlying risk factors. Heart disease and stroke, alongside cancer, remain the three leading causes of death and CVDs continue to be the leading cause of hospitalization in Canada.

Canadian and international research indicates that nine significant biomedical and behavioural risk factors account for the vast majority (90% or more) of the population attributable risks for myocardial infarction (heart attack) and stroke. These nine risk factors are abnormal lipids, smoking, high blood pressure, type 2 diabetes, abdominal obesity, psychosocial stress, limited or lacking consumption of fruits and vegetables, regular excess acohol consumption, and limited or lacking regular physical activity. However, a social determinants of health approach indicates also that material deprivation, along with psychosocial stress and the adoption of unhealthy coping behaviours are critical underlying risk factors to consider.

The DOHaD evidence indicates also that early life influences are highly significant and likely of greatest importance to those living in poverty in terms of nutritional factors (including inadequate fetal nutrition and nutritional imbalance) but also stress.

Although the nine traditional risk factors are considered to account for most of the CVD risk in a population and are thus crucial risk factors to control, there is increasingly clear evidence of impacts at a population level on CVD from environmental exposures such as particulate air pollution and lead (i.e., exposure among adults and perhaps due to lifelong exposure).

In addition to the CVD risk from low birth weight, congenital cardiac birth defects can also lead to later life CVD risk. These two outcomes are also associated with a wide variety of environmental exposures including air pollution and environmental tobacco smoke (ETS), certain solvents, pesticides and heavy metals. Additional early life exposures that may contribute to later life CVD risk including substances with endocrine disrupting potential, like BPA and lead.

Early Exposures and Diabetes

There is a high prevalence (6.2% among those ages one and older in 2006-07) and rising incidence of type 2 diabetes in Canada, within the context of a global pandemic of this disease. Rates of diabetes[1] are higher in Ontario compared to the Canadian national average and are distinctly higher among First Nations populations across Canada.

Obesity is a clearly linked, yet independent risk factor for type 2 diabetes. The dramatically rising obesity rates in Canada are, not surprisingly, paralleled by the increasing population statistics for diabetes. Excess food intake and insufficient physical activity on a population level are still viewed as important contributors to the secular trend to increasing obesity. However, experts indicate that several other risk factors, including exposure to endocrine disrupting chemicals, intrauterine environment and transgenerational factors, and social determinants of health, among others, provide plausible evidence of additional contributors to the global obesity pandemic.

1 90% of diabetes cases are Type 2 and the focus of this report. Henceforth, diabetes is intended to mean Type 2 diabetes.

Alongside genetic risk factors, there is considerable overlap among the economic, social and psychosocial risk factors for obesity, metabolic syndrome, diabetes and CVD. In addition, obesity and diabetes are themselves risk factors for other chronic diseases such as certain cancers, Alzheimer's disease, cognitive impairment, dementia, and CVD.

Evidence suggests that exposures to a broad range of environmental agents may disrupt insulin metabolism or alter biochemical activity in the pancreas, and be implicated in the onset of diabetes or of its related risk factors. Evidence is limited, largely cross-sectional in nature, and focussed on exposure during adulthood but has prompted studies in developing organisms that indicate endocrine disrupting compounds may act on genes during development in a manner that permanently affects the nature of adipose tissue and multiple metabolic processes in the body. These studies are instructive as to the possible associated diabetes risks from exposure to air pollution, lead, BPA, some phthalate metabolites, organophosphate (OP) pesticides and POPs (such as DDE, PCBs and dioxins).

The DOHaD framework and epigenetics contribute to understanding the role intrauterine conditions (e.g. fetal undernutrition or overnutrition; low birth weight, exposure to endocrine-disrupting substances) play in increasing risks for obesity and diabetes in later life.

The concept of endocrine-disrupting substances as "obesogens," was first described in 2006. Suspected obesogens are typically ubiquitous environmental chemicals that may act at very low levels of exposure and inappropriately influence the creation of fat cells and permanently affect the nature of adipose tissue, metabolic processes in the body and weight homeostasis. This body of evidence is largely accumulating from toxicological studies. Epidemiological studies are more limited and less consistent in their findings of obesogenic properties of environmental chemicals.

The list of possible obesogenic chemicals noted in recent reviews includes, DES, BPA, phthalates, organotins, PBDEs, polyfluoroalkyl chemicals, and POPs including OC pesticides and PCBs. Effects may occur by multiple mechanisms and may differ if exposure occurs *in utero* (during development) or during adulthood. The obesogen hypothesis proposes that the metabolic changes induced by environmental chemicals (i.e., altered fat differentiation or function and the initiation or misregulation of homeostatic controls) are superimposed on current trends of excess food intake and limited physical activity. This is an important area for further research, including a strong need for more compelling epidemiological data.

Early Exposures and Brain Impacts – Focus on Alzheimer's Disease and Parkinson Disease

Alzheimer's Disease (AD), and related dementias such as vascular dementia, as well as other neurodegenerative diseases such as Parkinson's Disease (PD) are considered part of a rapidly growing epidemic related to an aging population and the convergence of multiple risk factors. About 500,000 Canadians have dementia (about 63% is AD) and this number is predicted to be over 1.1 million in 2038. PD affects more than 100,000 people, a number predicted to double by 2050.

Advancing age is a key risk factor. The small proportion of AD associated with genetic risk factors typically manifests at an earlier age than other dementias of old age. Gender is a risk factor for AD in post-menopausal women. Strictly genetic risk factors account for about 5-10% of PD with the balance caused by complex gene-environment interactions that are not fully understood. Gender is a risk factor for PD with men having twice the risk as women. Research indicates that healthy brain aging results from a lifelong continuum beginning with healthy brain development and creation of brain reserve. Research indicates that healthy brain aging results from a lifelong process beginning with healthy brain development and creation of "brain reserve." Research into both AD and PD indicates that the timing and/or likelihood of their occurrence in old age results from a complex combination of lifelong influences ("multiple hits" and the "silent toxicity" or

latency of some risk factors), including epigenetic influences in the womb, that contribute to "brain reserve."

A continuum of common risk factors exists for obesity, metabolic syndrome, diabetes, CVD, AD and vascular dementia. Obesity may also be a risk factor for PD. Common risk factors include the same nine biomedical and behavioural risk factors noted for CVD as well as the additional risk factors noted for obesity and diabetes. Of particular importance among the common risk factors are those where circumstances contribute to inflammation and oxidative stress and thence to disrupted insulin signaling with some researchers calling AD "diabetes of the brain." Links to PD pathologies are more specific to effects of oxidative stress in the brain.

For environmental exposures in adults, insofar as a continuum is apparent whereby AD, and to a more limited extent PD, share common risk factors with other chronic diseases, the environmental exposures associated with these other conditions are also relevant. Recapping from the discussions about CVD and diabetes, these exposures include: air pollution, lead, BPA, phthalates, OP pesticides, and POPs.

Some adult exposures more directly implicated in AD include lead exposure (perhaps due to lifetime chronic exposure) and air pollution (also implicated in PD). Although there is less evidence, associations have been suggested with pesticides (PD via occupational exposure), PCBs and other POPs (AD, dementia/cognitive decline and PD), solvents (PD), and some additional metals (manganese, iron and copper with possible links to PD).

Likewise for early life exposures, the apparent continuum of several chronic conditions and diseases, including shared risk factors, is also relevant for AD and to some extent PD. Recapping early life exposures of concern in terms of being risk factors common to an apparent continuum of multiple chronic diseases, including AD, these exposures include: air pollution, organic solvents, chlorophenoxy herbicides, trihalomethanes, ionizing radiation, lead, ETS, mercury, OC and OP pesticides, nitrates in drinking water, arsenic, phthalates, BFRs, polyfluorinated compounds, BPA, phthalates, organotins, and PCBs.

Early life exposures for which there is more direct evidence of possible associations with later life neurodegeneration include air pollution (associations with AD, and to lesser extent PD) and lead (associations with AD).

Comparing the list of substances suspected in developmental neurotoxicity indicates considerable overlap with substance where evidence indicates associations with AD, PD or various conditions and diseases that may be co-morbid risk factors such as obesity, metabolic syndrome, diabetese and CVD.

Early Exposures and Cancer

Cancer represents a considerable chronic disease burden in Canada, having overtaken CVD as the leading cause of death. While cancer mortality is declining overall, it is predicted that nearly half of all Canadians will get cancer and approximately one in four will die from cancer. The most common cancers in Canada vary by gender and are breast, prostate, lung and colorectal cancers. Cancer agencies in Canada note increasing incidence in certain cancers (e.g. thyroid) and rising trends among adolescents and young adults, although cancer is still largely a disease of older adults.

Although influential work from the 1980s minimized the role of environmental factors in cancer causation, more recent research is seeking to correct that now outdated view. Genetic inheritance accounts for a small percent of cancers. Genetic polymorphisms may interact with environmental factors to influence human cancer causation. Additional processes affecting cancer susceptibility

such as cellular detoxification can be influenced by exogenous variables such as stress and nutrition, which are in turn affected by the broad SDOH.

There are many cancer risk factors, including the well known behavioural risk factors (smoking, diet, physical inactivity) along with others such as alcohol consumption, obesity, and social factors. A very large and growing body of evidence points also to multiple environmental and/or occupational exposures as known and/or suspected contributors to many different cancers, including those in highest prevalence.

Adding to the genetic mutation theories of cancer causation is expanding knowledge of the epigenetic mechanisms and events from the influence of external factors, including exposure to environmental contaminants. Epigenetic mechanisms are seen as central to understanding how cancers develop and progress. Furthermore, this knowledge indicates that these mechanisms are also centrally involved in early life events that can lead to later life cancer.

Molecular epidemiology, using biomarkers (such as cord blood levels of known carcinogens or their metabolites or cotinine from exposure to ETS), offers promise as an approach to detecting and preventing cancer development including those that result from early life exposures.

A wide range of chemical substances and physical agents are implicated in human carcinogenicity principally from studies of adults exposed occupationally or environmentally. The evidence for greater vulnerability of those exposed prenatally or in childhood to known or suspected carcinogens suggests two overall mechanisms: direct but delayed causation and increased sensitivity to later exposures.

There is evidence of early life exposure risk factors related to three highly prevalent cancers (breast, prostate and testicular cancers), which are a focus of this report.

For early life exposures and breast cancer, the greatest risks appear to come from large categories of substances suspected of endocrine disruption, either as xenoestrogens (i.e., foreign estrogens) or those with other endocrine disrupting properties. Substances of concern include POPs such as dioxins, PCBs, and most of the persistent OC pesticides such as DDT, its metabolite DDE, as well as dieldrin, aldrin, heptachlor and chlordane. Other less persistent xenoestrogenic substances, like BPA, are implicated on the basis of animal studies for increasing breast cancer risk. More limited evidence exists for links to breast cancer from exposure to alkylphenols, several metals, phthalates, parabens, UV filter components of sunscreens and the food additives bovine somatotropin (rBST) and zeranol.

Experts describe the potential for these substances to exert permanent epigenetic changes (during mammary gland development *in utero*) that alter later susceptibility, often before and during puberty, to other factors that can initiate breast cancer.

Based on occupational studies, some evidence for increased risks of prostate cancer, possibly via endocrine disruption mechanisms, implicates some pesticides, PCBs and cadmium. There is also evidence linking early life exposure to the synthetic hormone DES and to BPA to later prostate cancer via endocrine-disrupting modes of action.

Epidemiological and toxicological evidence supports the hypothesis that disruptions in sex hormones, occurring during fetal development, play a role in the current increasing incidence of testicular cancer, and of genital abnormalities in boys. Experts have suggested a broader range of risk factors, including environmental exposures, as being involved in the etiology of the developmental disorder called testicular dysgenesis syndrome (TDS) which they postulate is an indicator also of testicular cancer risk.

The TDS concept is a unifying hypothesis that invokes a common fetal origin of four effects on the male reproductive system, including the birth defects cryptorchidism (undescended testicles) and hypospadias (brith defect in the male urinary tract), poor semen quality and the later development of testicular cancer. Multiple animal studies have demonstrated these effects from endocrine

disrupting chemicals. Some pesticides, certain phthalates, perfluorochemicals and bisphenol A may all disrupt fetal testes development and are implicated in the development of TDS.

Early Exposures and Respiratory Disease

Although likely a large underestimate, prevalence of certain physician-diagnosed respiratory diseases in Canada is very high, most prominently asthma (2.74 million), chronic obstructive pulmonary disease (COPD) (>754,000), and lung cancer (>20,000). The focus in this report is on asthma due to high prevalence, evidence of associations with early environmental exposures (along with other risk factors), and because it is the most common chronic illness in children. Doctor-diagnosed asthma affects approximately 10% of Canadian children aged 2-7 years, almost quadruple the prevalence from 20 years earlier.

Asthma has been found to affect more male children (possibly because of smaller lung size, but fewer adult males (possibly because of larger lung size). While asthma may improve with puberty, some children go on to experience lifelong effects. The prevalence among adult women has been increasing, particularly in early to late middle age (35-64 years), and in adult men aged 35-44. Those with chemical hypersensitivity seem disproportionately affected by asthma, especially with onset during in adolescence (age 11-20 years).

There are complex host, genetic, and environmental risk factors for asthma with multiple interactions. Although the cause of asthma has not been fully elucidated, an immunological response to aeroallergens, resulting in inflammation of the lung airways has been noted.

Environmental factors modifying the epigenome in early life appear to play a crucial role in the susceptibility to asthma development. At least two windows of vulnerability for epigenetic changes are apparent. These include possible environmentally-induced changes *in utero* affecting how fetal genes are expressed, thus influencing later allergy and asthma risk. Then in early life, further epigenetic changes may occur if environmental factors modify a child's genome potentially causing and/or prolonging allergy or asthma.

Lung development begins in early pregnancy and continues to about age 18. It is vulnerable to developmental interruptions if there is exposure to environmental risk factors *in utero* or inhaled after birth. Greater exposure, compared to adults, occurs in infancy and early childhood for multiple physiological and behavioural reasons.

Potential mechanisms for how pollutant/chemical exposures can have a lifelong influence on lung structure and function include interference with factors in developmental processes in the lungs and the immune system that are highly conserved across species such as gene regulation, molecular signaling, and growth factors involved in branching morphogenesis and alveolarization. This evidence sits within the DOHaD model including evidence that lifelong lung function in both asthmatics and non-asthmatics is influenced by early life events such as low birth weight, undernutrition, and other factors.

There is evidence that interactions between genetic and environmental factors in infants and young children result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.

Multiple genes govern multiple aspects of the immune and respiratory systems, there is a great deal of heterogeneity among individuals, and variation also by gender and age. Epidemiological evidence reveals that genetic susceptibility for asthma or allergies onset can be influenced by multiple gene-environment and gene-gene interactions, as well as epigenetic mechanisms. For example, interactions between genetic and environmental factors in infants and young children

result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.

Evidence for associations between specific environmental risk factors and asthma are often inconsistent. Environmental risk factors related to asthma that are supported by considerable evidence include exposure to biological natural inhalants, childhood viral infections, ETS, other indoor and outdoor pollutants, socioeconomic status and stress, as well as to nutritional factors, gut colonization, and obesity (which influence immune system development).

Evidence indicates heightened risk of asthma onset in children when exposure to outdoor air pollution occurs in combination with high parental stress.

A wide range of outdoor air pollutants, such as CACs and many PAHs, acid vapours and aerosols, and diesel exhaust are associated with asthma onset and are triggers of asthma attacks.

Indoor air pollutants may overlap with outdoor and include products of combustion such as NO_2 and CO, formaldehyde, and numerous VOCs arising from consumer products such as cleaning agents, laundry, and personal care products.

Children are exposed to complex mixtures of pollutants indoors and out, and there are enormous challenges in assessing the health impacts of many co-exposures, as well as cumulative exposures. Nevertheless, there is evidence of association between preterm birth and air pollution, which in turn affects lung development. Air pollutants also impact the immune system, some skewing it towards T_H2 cell production.

Phthalates and BPA, well-known for their endocrine disrupting effects, have also been shown to heighten lung inflammation, and there is some evidence of immunotoxicity related to exposure to perfluorinated compounds.

Overall Conclusions

This report was one of several activities that fulfilled a vital objective for a larger project: to learn from each other across the CPCHE and OCDPA networks and to integrate each other's knowledge about risk factors for chronic disease. Despite its length, it only scopes a vast amount of research but now provides a foundation for further detailed work including analysis of related policy issues.

It revealed a number of truths about chronic disease prevention. The perspectives and approaches to population health prevention represented by the two networks (CPCHE and OCDPA) are similar in their great complexity. There is far more complexity involved than implied when chronic disease response strategies than is implied in or amenable to response strategies focused solely on individual behavioural changes.

The challenges to be faced over the next two to three decades in addressing chronic disease are sobering given the numbers of people predicted to be affected and estimates of costs. In multiple reports, dramatic language is used to frame these predictions such as the "rising tide" of dementia, the "perfect storm of risk factors" for CVD, the epidemic of obesity and diabetes and a related "economic tsunami" of health care costs, and "no breathing room" to capture the high numbers of illness and death and very high cost of air pollution. For cancer, the hard statistics (nearly half of Canadians will get cancer and about one in four will die from it) leave no need for the dramatic language.

These predictions and this language are used against the backdrop of an aging population. Within another 20 to 30 years, one quarter of Canada's population will be senior citizens (over the age of 65). If current trends continue, over 80% of those seniors will have one or more chronic disease. This disease burden will be disproportionately felt by those live in poverty. Many severe health impacts of climate change are expected to occur in coming decades. Similarly dramatic language, equally justified, arises. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health – air, food, water and shelter.

Because of the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures explored in this report, a broader approach to prevention is worthwhile. Equally important is a critical need to address the "causes of the causes," notably poverty and the SDOH given the reality of biomedical and behavioural risk factors for various diseases arising from social and economic conditions.

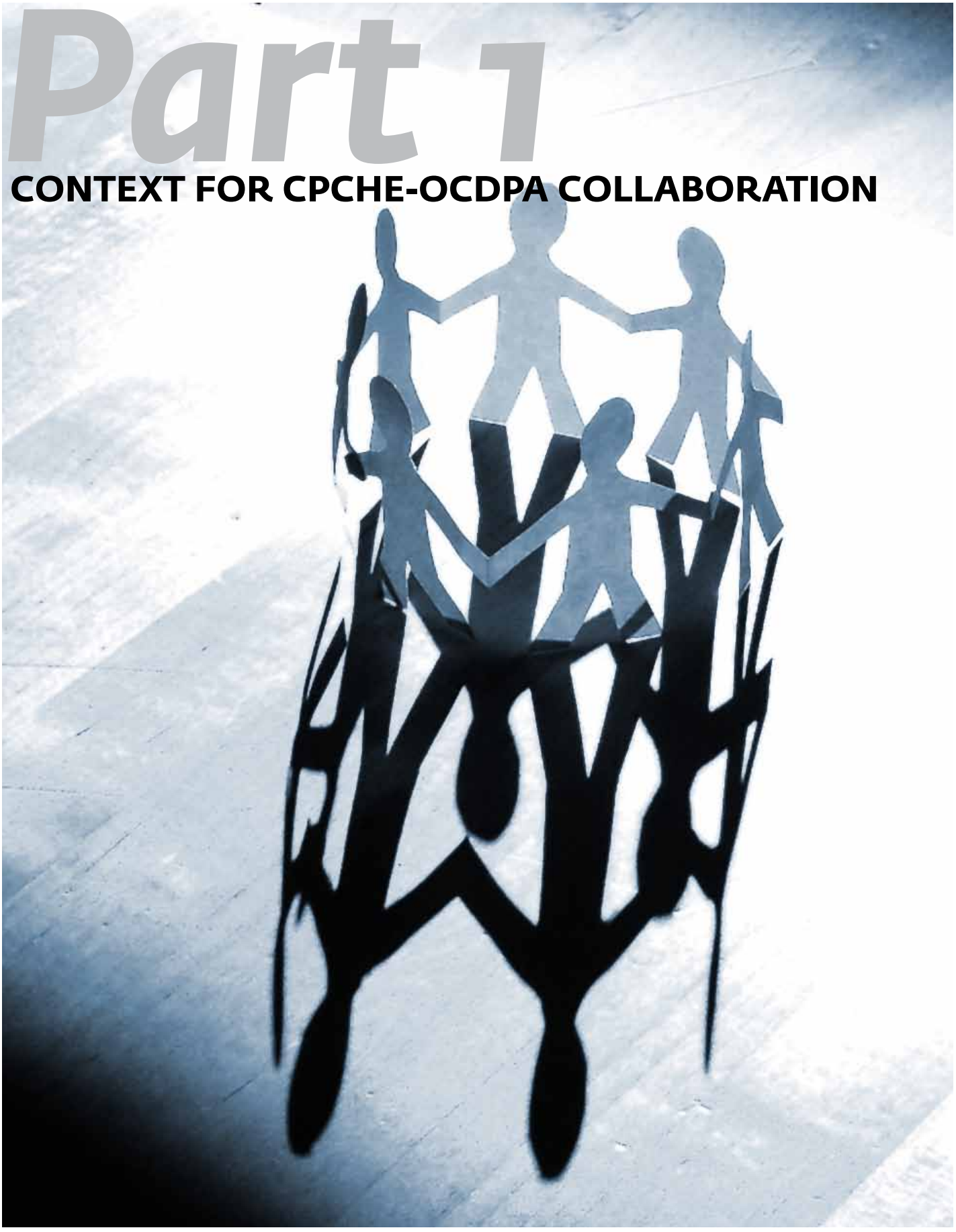
Environmental influences on health are similarly multifaceted, involving multiple pollutants, exposure routes, on a scale ranging from macro to micro (e.g., from built environment features to the loading of floor dust with toxic substances), multiple interrelationships, and life course vulnerabilities. Biomonitoring data indicates population-wide exposure to multiple contaminants, with levels higher in children and generally highest in breast-fed infants, with unknown consequences.

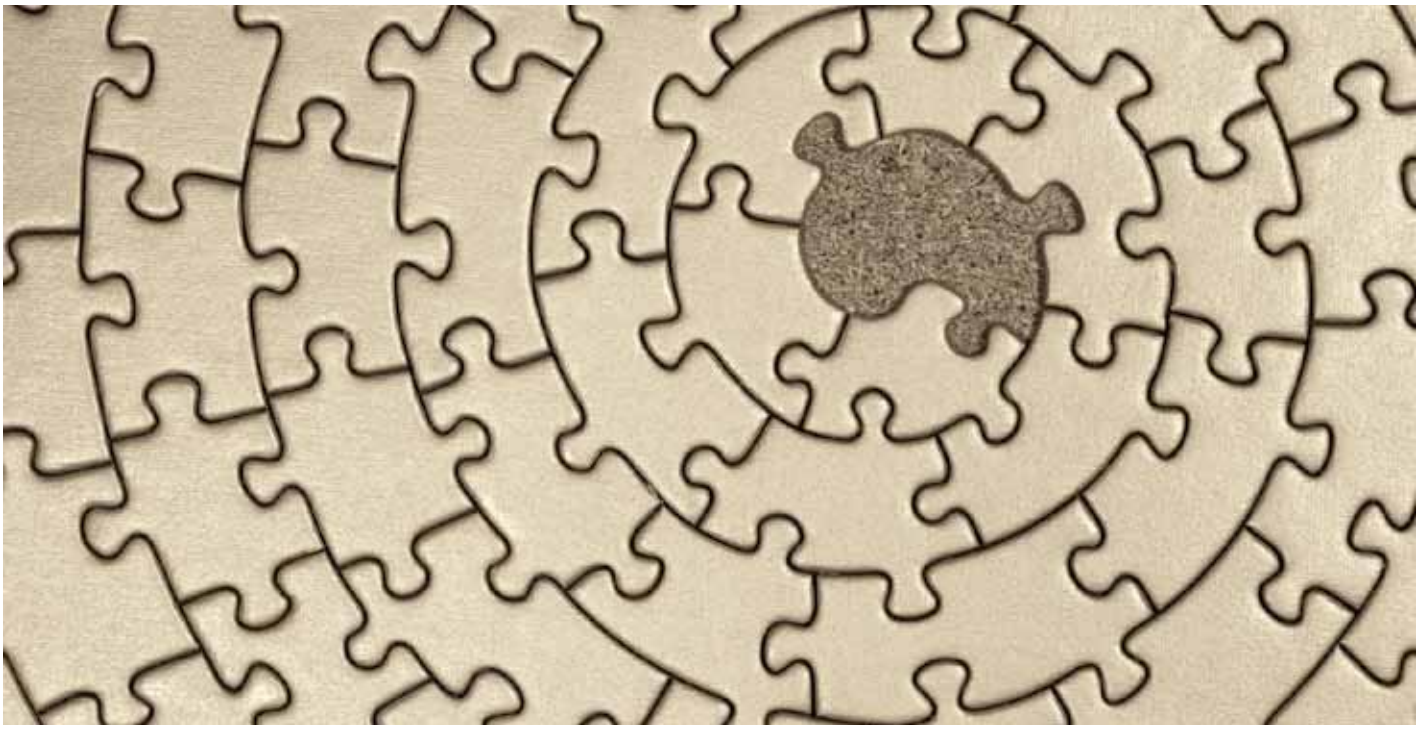
It is already well-established that the *in utero* and perinatal "environment" and maternal and early childhood circumstances play major roles in the risk of later life disease. Within this new paradigm for disease causation, the DOHaD concept and the related field of epigenetics, a rapidly expanding body of research indicates a role for early life exposure to environmental contaminants in this lifelong continuum of disease vulnerability.

Because of the abundant complexity, not only is there a need for more research, but also to adjust assessments of the strenghth of evidence for associations between risk factors and health outcomes via tools such as the Bradford Hill criteria and hierarchical models of study designs. Given the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures, a broader approach to prevention is worthwhile. Table 1 above provides a summary of early exposures (*in utero* or childhood) for which there is evidence of associations with prevalent chronic diseases addressed in this review. It is important to emphasize that important detail about strength of evidence (explored throughout this report) is not included in this table. Nevertheless, the multiple exposures noted indicate a priority list of substances of concern particularly those that repeat frequently across the table including air pollution (notably the CACs), lead, multiple pesticides, multiple POPs including PBDEs, phthalates and BPA.

Part 1

CONTEXT FOR CPCHE-OCDPA COLLABORATION





1.0 Introduction and Scope

This report is the product of a "network to network" collaboration among the member organizations of the Canadian Partnership for Children's Health and Environment (CPCHE) and the Ontario Chronic Disease Prevention Alliance (OCDPA). The overall purpose of working together is to exchange knowledge and identify opportunities to advance mutually-reinforcing objectives to achieve children's environmental health protection and chronic disease prevention. Hence, this report is about integrating, in some cases further integrating, children's environmental health issues into the public health response to chronic disease. That response is multi-dimensional, arises from a broad perspective on the multiple determinants of health, and is fundamentally about *prevention* of chronic disease. This report is equally about incorporating a broad perspective on the multiple determinants of health into the societal response to fetal and/or childhood exposures to chemicals and pollution.

CPCHE and OCDPA together comprise more than 35 organizations and share one organization in common, the Ontario Public Health Association. Also shared are concerns about five chronic diseases affecting large numbers of people (cancer, diabetes, cardiovascular, respiratory and neurodegenerative diseases or conditions), the risk factors related to these diseases, and a common desire to seek the means of preventing them.

CPCHE and OCDPA share an understanding of the importance of three risk factors for many chronic diseases: smoking, unhealthy eating and physical inactivity. However, in broadening the understanding of risk factors to include the social determinants of health and environmental factors, a rich and complex landscape of issues is explored in this collaboration.

In working together, including developing new relationships among the groups involved across these two "networks," challenges arise with both terminology and scope.

With respect to terminology, CPCHE addresses traditional environmental issues such as air quality or the use of pesticides. However, the word "environment" inadequately captures the meaning or focus of one of CPCHE's key concerns, chemical exposures from consumer products, such as exposure to bisphenol A from canned food. Likewise, the focus on "child" health and the project focus on "early environmental exposures" includes exposures that can occur prior to conception,

in utero and postnatally through to the end of adolescence. As well, a focus on chronic "disease" might exclude certain medical or biophysical conditions of relevance to this collaborative effort including, for example, obesity, and a broad range of learning and behavioural problems in children.

In terms of scope, issues addressed by CPCHE include a broad range of potential exposure sources across highly varied developmental stages (preconception, prenatal, childhood and adolescence). Many different health concerns are at stake including asthma, cancer, learning and behavioural problems, low birth weight, birth defects and endocrine disruption. Alongside these multiple fields of scientific inquiry, there is an equally broad policy realm. An equally broad scope of issues is addressed within the OCDPA. When considering the combined context of the multiple determinants of health and across the entire life course, particularly during mid-life and the elder years, there is a still broader range of health concerns and policy responses. Neither group is new to these issues. Evidence-informed decisions have already been made within both CPCHE and OCDPA as to the choice of priorities and areas of strategic focus.

This collaborative effort begins with this foundation of evidence-informed priorities within CPCHE and OCDPA. Notably, the choice to focus on six specific chronic diseases meant leaving out detailed consideration of the multiple risk factors, including environmental exposures, for low birth weight, birth defects and neurodevelopmental disorders of prenatal or postnatal origin, all of which can result in multiple chronic conditions. These areas are addressed to some extenet insofar as they relate to the chronic diseases and conditions discussed. They remain key areas of focus for CPCHE partners despite not being able to address them in greater detail herein. Nevertheless, the scope of issues to address remains very large in order to investigate the intersection of early environmental exposures and chronic disease.

A key starting point is recognition that the environmental contribution to the incidence of chronic disease is only beginning to be elucidated or empirically measured. The evidence reviewed in this report indicates that environmental factors play a role alongside other chronic disease risk factors or social conditions. Complex interactions are also apparent, particularly when including recognition of the often closely related impact of poverty on health. It is increasingly apparent that there are developmental origins of lifelong health that can be significantly influenced by socioeconomic status. Likewise, the evidence explored herein points to lifelong effects of developmental exposure to environmental contaminants.

Hence, the end result of taking on such a vast topic is ultimately a scoping review of the evidence. This report clarifies and documents the known and suspected linkages between early exposures and chronic disease outcomes within the context of the multiple determinants of health. In seeking to increase our collective knowledge about these linkages, CPCHE and OCDPA can now use this review as a foundation for further work in specific areas of environmental exposures and chronic disease. This foundation also enables the two networks to undertake related policy analysis and to make recommendations accordingly.

1.1 Towards an Integrated Response to Chronic Disease

To address chronic disease prevention and healthy living, the OCDPA has envisioned a province-wide system that enables effective coordinated planning, delivery and continuous improvement of health promotion and chronic disease prevention interventions at a population level. In the "Thinking Like a System" (2006) report, the OCDPA proposes a chronic disease prevention system of six elements (the "what" of chronic disease prevention) and three crosscutting processes (the "how" which are essential to the system).[2] Through this systems approach, the OCDPA addresses behavioural risk factors (e.g. high-risk alcohol consumption, physical inactivity, poor mental health, tobacco use, unhealthy eating) and social determinants of health (e.g. income, education, employment, housing, food and inclusion) which contribute to chronic disease risks.

2 The six elements are: capacity development; best practices identification; research; surveillance and monitoring; evaluation; policy and program implementation. The three processes are: planning and coordination; knowledge exchange; advocacy. More details: http://www.ocdpa.on.ca/rpt_SystemPlan.htm

CPCHE's research has also identified a range of chronic diseases and conditions as being of greatest significance to the environmental health of children and as an influence on lifelong health. CPCHE also recognizes the importance of the multiple determinants of health. In addressing prevention, CPCHE focuses on reducing or preventing exposure to toxic chemicals and pollutants. Given the large numbers of such exposures, key criteria for choosing where to focus CPCHE's attention have included 1) addressing those health conditions where large and/or growing numbers of children are potentially affected, 2) focusing on environmental exposures associated with those same health conditions, and 3) an additional emphasis on conditions that are serious and/or irreversible in nature. This approach has resulted in an evidence-informed focus on respiratory disease, impacts on the brain, and endocrine disruption, particularly as the latter relates to a range of other health outcomes including cancer and reproductive and/or developmental toxicity.

Key lessons learned across this network to network collaboration point to the need for CPCHE to address additional chronic diseases and conditions and for OCDPA to include environmental exposures in its systems approach. CPCHE's focus on the situations and circumstances that can increase exposures, notably poverty, can be broadened by OCDPA's more fulsome perspective on the importance of the social determinants of health. With both OCDPA and CPCHE recognizing the wisdom of a population health approach, and given the large numbers of children living in poverty in Canada, prevention of poverty and the need to address related social determinants of health represent key areas of mutual concern between OCDPA and CPCHE.

1.2 Methods

This report was informed by regular meetings of a Steering Committee comprised of members of CPCHE and OCDPA partner organizations with expertise in researching, analyzing and summarizing the public health, medical, scientific, legal and policy dimensions of environmental exposure and chronic disease.

Summaries of evidence on associations between early environmental exposures and chronic disease were compiled from a review of available literature but within certain key limitations. Given the broad scope of the project and within time and resource constraints, this report does not summarize a full scientific literature review into multiple disease endpoints and potentially thousands of chemicals or environmental pollutants. Rather it is more of a scoping review. It relies in large measure upon research compiled in comprehensive reviews, syntheses and meta-analyses published by credible, authoritative and unbiased sources in peer-reviewed scientific publications. This survey of existing reviews included direct reference to some but not all, of the literature cited in each. It was also supplemented by keyword searching for additional scientific articles, focused again on reviews, using standard internet search engines. Another important source of information was material posted to the multiple websites of partner organizations within both of CPCHE and OCDPA as well as information provided on-line by government agencies. A similar approach was taken to research the literature on chronic disease prevention and the social determinants of health.

An overarching objective was to assist CPCHE and OCDPA in understanding the strength of evidence of associations between early exposures and chronic disease. While a related objective was to use this review to identify opportunities for policy reform and exposure prevention suggested by the evidence, the scope of work proved too large for the time available. Hence, the two networks concluded the work with a discussion of future steps to address mutually-reinforcing activities aimed at policy issues.

Peer review occurred first via internal distribution of draft manuscripts to staff and expert advisors among the member organizations of both CPCHE and OCDPA drawing upon multi-disciplinary expertise. External review of the revised draft report was provided by physicians with well-recognized strengths in literature review, appraisal and synthesis, as well as in environmental and occupational clinical medicine.

1.3 Introduction and Scope – Key Points

- This report is a product of a network to network collaboration that provides a foundation for advancing mutually-reinforcing chronic disease prevention objectives.
- CPCHE and OCDPA can build on their existing knowledge and priority setting, learn from each other and integrate each other's knowledge about risk factors for chronic disease.
- CPCHE member organizations have stated there is a need for primary focus on poverty reduction since it is known to add to the exposure burden for children but can learn from OCDPA's more fulsome perspective on the importance of the social determinants of health.
- OCDPA organizations utilize a systems approach that contains clear recognition of the social determinants of health, notably poverty, as key determinants of health that must be addressed to address chronic diseases. However, environmental exposure is a missing/ incomplete piece of this approach.
- The project scope is very large, for literature on the multiple determinants of health, on individual chronic diseases, and on effects of environmental exposures. Hence, research methods included a focus on existing literature reviews and undertook a scoping review of the evidence versus a full scientific literature review.

2.0 Chronic Disease and Care in Canada's Aging Population

Chronic diseases are those of long duration, generally slow progression, and are caused by multiple risk factors.[3] In describing chronic diseases as a whole, the World Health Organization notes the following common characteristics:

- Chronic disease epidemics take decades to become fully established – they have their origins at young ages;
- Given their long duration, there are many opportunities for prevention;
- They require a long-term and systematic approach to treatment; and
- Health services must integrate the response to these diseases with the response to acute, infectious diseases.[4]

The chronic diseases considered in this report constitute a large and increasing burden on society. The term "chronic disease" encompasses a wide range including, most commonly, cardiovascular disease, cancer, chronic respiratory diseases, and diabetes. Other chronic diseases can include vision and hearing impairment, kidney disease, and various neuropsychiatric and neurodegenerative, bone and joint, environmental sensitivity and genetic conditions.

For people over the age of 65 residing in Canada, about 80 percent have one chronic disease, and of those, about 70 percent suffer from two or more chronic diseases.[5] In Ontario, about one in three people (all ages) have one or more chronic diseases[6] and at least 60 percent of Ontario's health-care costs are due to chronic diseases.[7]

Table 2 provides a summary of available Canadian data on the impact of six chronic diseases in terms of prevalence, cost estimates and, where relevant, mortality rates. Both the prevalence in

3 World Health Organization (2010) *Global status report on non-communicable diseases 2010*.
4 World Health Organization and Public Health Agency of Canada (2009) *Preventing Chronic Diseases – A Vital Investment*.
5 Gilmour H and Park J (2005) Dependency, chronic conditions, and pain in seniors. *Health Reports*; 16(Suppl):21-31. Statistics Canada, Catologue No. 82-003
6 Health Council of Canada (2007) Why health care renewal matters: Lessons from diabetes - Toronto, Ontario. Data derived from: Canadian Community Health Survey, 2005, Statistics Canada - Ottawa.
7 Ontario Health Quality Council (2007) 2007 Report on Ontario's Health System.

the Canadian population and the cost estimates are very high – in the multi-millions of people and multi-billions of dollars. Most experts emphasize that such cost estimates are conservative. It would be inaccurate to create a tally of estimated total chronic disease costs from the estimated costs of the six chronic diseases since data are not directly comparable for a variety of reasons, e.g., due to differences in time periods for cost estimates and/or dissimilar data gathered for each disease, and also because individuals may have more than one disease, which could result in double counting in certain aspects of the estimated costs.[8]

It is noteworthy that indirect costs from chronic disease can be many times higher than direct costs. For example, family caregivers are the hidden backbone of the health and long-term care system in Canada contributing over $5 billion dollars of unpaid care.[9] One-in-five Canadians, age 45 and over, are providing some form of care to seniors with long-term health problems. Therein, 43 percent of informal caregivers are between the ages of 45 and 54 years. Caregivers often balance this role with job and family responsibilities and are disproportionately comprised of women. As well, over 200,000 caregivers are over the age of 75.[10] In addition to the estimates of economic burden of chronic disease provided in Table 2, a recent report estimates that the annual economic burden of obesity between 2000 and 2008 increased by $735 million from $3.9 to $4.6 billion. The analysis included direct costs to the health care system and indirect costs to productivity (including loss of economic output due to premature death and short- and long-term disability) related to eight chronic diseases.[11]

consideration for chronic disease prevention efforts. Currently, 13 percent of the population in Canada are seniors (age 65 and up). In about 25 years, that figure is anticipated to nearly double (to 25 percent by 2036) due to increased longevity and lower birth rates. This demographic shift, combined with the fact that most seniors suffer from at least one chronic disease, provides a strong incentive to prevent chronic disease throughout the life course.

Moreover, an increasing number of children are experiencing chronic diseases, or conditions that lead to chronic diseases. For example, (as discussed in more detail in Section 13), asthma and other respiratory conditions in childhood are associated with permanent deficits in lung growth and function.[12] Although cancer in children remains rare, and survival from the most common childhood cancers is increasingly the case,[13] childhood cancer can lead to additional health complications, including but not limited to more cancer, later in life. Since the late 1970s, the prevalence of overweight and obesity has increased dramatically among youth in Canada.[14] People who are overweight or obese have higher risks of developing chronic diseases and other conditions, as further discussed in Sections 9 – 11. Large numbers of children experience a wide range of neurological and/or behavioural conditions that are assuredly chronic in terms of their lifelong influence on the ability to cope in society or in some cases to live independently.[15] As well, low birth weight and preterm births are understood to be indicators of potential lifelong consequences (as discussed throughout this report). Incidence of preterm birth in Canada (excluding data from Ontario) has been rising steadily for 20 years, from a rate of 6.4% in 1981 to 7.9% in 2004 although this increase has been mainly attributed to a rising incidence in multiple births.[16,17]

Despite some improvements in health trends in recent years such as survival rates for cancer or advances in treating heart disease, not all health trends are improving. In particular, the growing

8 Ontario Chronic Disease Prevention Alliance (2007) Economic Costs of Chronic Disease in Canada, 1995-2003.
9 Fast J (2002) A profile of Canadian chronic care providers. Final report submitted to Human Resources and Development Canada.
10 Cranswick K and Dosman D (2008) Eldercare: What We Know Today. Component of Statistics Canada *Canadian Social Trends,* Catalogue no. 11-008-X.
11 Government of Canada (2011) *Obesity in Canada: A Joint Report from the Public Health Agency of Canada and the Canadian Institute for Health Information.*
12 Kim JJ (2004) American Academy of Pediatrics, Committee on Environmental Health. Policy Statement. Ambient air pollution: health hazards to children. *Pediatrics*; 114:1699–1707.
13 Canadian Cancer Society's Steering Committee. (2009). Canadian Cancer Statistics 2009. Toronto: Canadian Cancer Society.
14 Shields M (2006) Overweight and obesity among children and youth. *Health Reports*; 17(3):27-42. Statistics Canada, Catalogue 82-003.
15 Learning Disabilities Association of Canada (2005) Putting a Canadian Face on Learning Disabilities. http://www.pacfold.ca/index.shtml
16 Shah P and Ohlsson A (2002) *Literature Review of Low Birth Weight, Including Small for Gestational Age and Preterm Birth.* Evidence-Based Neonatal Care and Outcomes Research, Department of Pediatrics, Mount Sinai Hospital for Toronto Public Health.
17 Ohlsson A and Shah P (2008) *Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence*. Institute of Health Economics (IHE) Report. Alberta, Canada.

prevalence of obesity and diabetes in Canada is predicted, if unchecked, to possibly result in the current generation of children being the first to have a shorter life expectancy than their parents.[18]

2.1 Cost Estimates for the Environmental Contribution to Chronic Disease

The World Health Organization (WHO) has estimated that 24% of the global disease burden and 23% of all deaths can be attributed to environmental factors.[19] They also found that children are more susceptible to this environmental health burden noting that, among children 0-14 years of age, the proportion of deaths attributed to the environment was as high as 36% (though in the context of this report it must be recognized that a large fraction of these deaths are due to lack of water sanitation and other factors not typical of developed countries). Globally, the estimated burden attributable to environmental exposures is as follows: 44% of asthma, 16% of cardiovascular disease, 19% of all cancers, 42% of COPD and 13% of neuropsychiatric disorders.[20]

The aging of the population in Canada and other industrialized countries is an important In Canada, the annual disease burden attributable to environmental exposures have been estimated[21] as follows:

- Respiratory disease (1050-3100 deaths; 34,000-93,000 hospitalizations; and 200,000-570,000 patient-days spent in hospital);
- Cardiovascular disease (5500-11,000 deaths; 33,000-67,000 hospitalizations; and 291,000-583,000 patient-days spent in hospital);
- Cancer (3400-10,200 deaths; 8000-24,000 new cases of cancer diagnosed; 11,000-32,000 hospitalizations; and 104,000-312,000 patient-days spent in hospital); and
- Congenital affliction (72-360 deaths; 128-640 serious congenital anomalies; 300-1500 hospitalizations; 2000-10,000 patient-days spent in hospital; and 500-2500 low birth weight babies).

Like the cost estimates noted in Table 2, the estimated economic impact in Canada of this environmentally-attributed disease burden appears to be significant. The authors applied a WHO methodology for determining the "environmentally attributable fraction" (EAF) of disease. They note that their results were initial and conservative estimates of the annual costs in Canada of four major categories of diseases. They concluded that between $3.6 and $9.1 billion is spent each year on respiratory disease, cardiovascular disease, cancer and congenital affliction associated with environmental exposures.

Both the Ontario Medical Association and the Canadian Medical Association have periodically estimated the economic cost of death and ill health from air pollution. The most recent estimates for Ontario attribute $3.6 billion in annual economic damages from air pollution as a result of health effects (including lost productivity, healthcare costs, quality of life, and loss of life).[22]

18 Butler-Jones D et al (2008) *The Chief Public Health Officer's Report on the State of Public Health in Canada*. Ottawa.

19 Prüss-Üstün A and Corvalán C (2006) *Preventing disease through healthy environments. Towards an estimate of the environmental burden of disease*. World Health Organization.

20 Includes neuropsychiatric disorders such as Alzheimer's disease and other dementias, bipolar affective disorders, Parkinson's disease, schizophrenia, epilepsy, alcohol use and drug use disorder, multiple sclerosis, insomnia, migraine, panic disorder, post-traumatic stress disorder, and lead-induced mental retardation.

21 Boyd DR and Genuis SJ (2008) The environmental burden of disease in Canada: Respiratory disease, cardiovascular disease, cancer, and congenital affliction. *Environmental Research*; 106:240-249.

22 Canadian Medical Association (2008) *No Breathing Room - National Illness Costs of Air Pollution*.

Table 2: Summary of Available Canadian Data on Prevalence, Cost Estimates and Deaths [23,24], Associated with Six Chronic Diseases

CARDIOVASCULAR DISEASE[25,26] For many years, the leading cause of death in Canada. As of 2007, now second, after cancer.		
Prevalence In 2007: • 1.3 million (4.8% of Canadians) living with heart disease In 2009: • 315,000 living with effects of a stroke	**Cost Estimates** Canada: $22.2B (Direct costs: $7.6B; Indirect costs: $14.6B) in 2000 $3.6B in 2000 (health care and lost productivity due to death and long-term disability caused by stroke)	**Deaths** In 2007: • Total: 69,503 deaths roughly split by gender with numbers for women slightly higher • Cancer and CVD responsible for 59% of all deaths
DIABETES[27] As of 2005, sixth leading cause of death in Canada, of which 90% is Type 2 and affects over two million Canadians.[28]		
Prevalence • Expected to double between 2000 and 2010, from 1.3 million (~4.2% of the population) to about 2.5 million (~7.3% of pop'n) • True prevalence likely higher since an estimated 700,000 also with the disease are undiagnosed. • From 2010 to 2020, 1.2 million more people likely to be diagnosed, about 3.7 million or 9.9% of the population.	**Cost Estimates (direct and indirect costs)** • Estimated at about $12.2 billion in 2010, an increase of $5.9 billion or nearly double the level in 2000. • Expected to rise by another $4.7 billion by 2020. • Direct cost of diabetes now accounts for about 3.5% of public healthcare spending in Canada. • Indirect costs are typically about 5 times greater than direct costs.	**Deaths (serious complications and premature death)** • 80% die from heart attack or stroke • 42% of new kidney dialysis patients in 2004 • Leading cause of blindness • 7 of 10 non-traumatic limb amputations result from diabetes complications • 25% of diabetics suffer from depression • Life expectancy shortened by up to 15 years for people with type 1 and 5 to 10 years for people with type 2 diabetes
CANCER[29,30,31,32,33] As of 2007, leading cause of death in Canada		
Prevalence In 2007: • 164, 711 new cases with prevalence of people living with cancer much higher	**Cost Estimates** Canada: $14.6B in 1998 Direct costs: $2.8B (incl. $1.8B in hospital care) Indirect costs: $11.8B (incl. Long-term disability: $962M; Short-term disability: $174M)	**Deaths** In 2007: • 69,595 deaths • Mortality rates indicate that 24% of women and 29% of men, approximately 1 in 4, will die from cancer

23 Statistics Canada. *Ten leading causes of death, Canada, 2004 and 2005*. CANSIM Table 102-0561.
24 Statistics Canada (2010) *Mortality, Summary List of Causes 2007*. Catalogue no. 84F0209X
25 Public Health Agency of Canada (2009) *Tracking Heart Disease and Stroke in Canada*.
26 Public Health Agency of Canada (2011) *Tracking Heart Disease and Stroke in Canada; Stroke Highlights 2011*.
27 Canadian Diabetes Association (2009) *An economic tsunami – the cost of diabetes in Canada*.
28 Public Health Agency of Canada (2008) *Report from the National Diabetes Surveillance System: Diabetes in Canada*. Ottawa, Canada. Report No.: HP32-2/2006.
29 Statistics Canada (2010) *Cancer Incidence in Canada 2007 and 2008*. Catalogue no. 82-231-X
30 Canadian Cancer Society's Steering Committee (2009) *Canadian Cancer Statistics – 2009*. Toronto, ON: Canadian Cancer Society.
31 Health Canada (2002). *Economic Burden of Illness in Canada, 1998*.
32 Canadian Cancer Society's Steering Committee (2010) *Canadian Cancer Statistics – 2010*. Toronto, ON: Canadian Cancer Society.
33 Canadian Cancer Society's Steering Committee (2011) *Canadian Cancer Statistics – 2011*. Toronto, ON: Canadian Cancer Society.

RESPIRATORY DISEASE[34] As of 2005, 4th leading cause of death (including chronic lower respiratory disease, influenza and pneumonia)		
Prevalence in 2007 Over 3 million with respiratory diseases (e.g. asthma, chronic obstructive pulmonary disease, lung cancer, tuberculosis and cystic fibrosis) Total number may be much higher; since no data for other conditions such as influenza, pneumonia, bronchiolitis and respiratory distress syndrome. 2.74 million with asthma, 754,000 with COPD and over 20,500 cases of lung cancer	**Cost Estimates** [35] Canada: $8.5B in 1998 Direct costs: $3.5B (incl. $1.5 billion in hospital care) Indirect costs: $5 billion (incl. Long-term disability: $985M; Short-term disability: $2.4B) Costs include: Acute Respiratory Infections, Pneumonia & Influenza, COPD and Asthma.	**Deaths** In 1998: 38, 081 deaths (incl. lung cancer -16,261, COPD – 9,398, influenza and pneumonia – 9,098).
ALZHEIMER'S DISEASE[36],[37] As of 2005, the eighth leading cause of death in Canada.		
Prevalence in 2010 Estimated 500,000 with AD or a related dementia (1 in every 11 over age 65). Over 70,000 are under 65, and approx. 50,000 under age 60. Almost three-quarters of those with AD are women Total predicted to be over 1.1 million by 2038 (2.8% of the population).	**Cost Estimates** Total economic burden (direct and indirect costs) estimated at approx. $15 billion in 2008 (of which $8B is direct and $7B is indirect costs). By 2038, annual economic burden predicted to be over $152B Cumulative economic burden predicted to be over $872B including a 10-fold increase in demand for long term care	**Deaths** As of 2005, 2.5% of Canadians died of Alzheimer's disease
PARKINSON'S DISEASE[38]		
Prevalence in 2010 Approximately 100,000 Canadian	**Cost Estimates** Canada: $558.1M Direct: $87.8M Indirect: $470.3M	**Deaths** Ontario study[15]: overall mortality odds ratio of 2.5 as compared with that among age-matched control subjects.

34 Public Health Agency of Canada (2007) *Life and Breath: Respiratory Disease in Canada.*
35 Health Canada (2002) *Economic Burden of Illness in Canada, 1998.* Catalogue. No. H21-136/1998 Ottawa.
36 Alzheimer Society of Canada (2010) *Rising Tide: The Impact of Dementia on Canadian Society.*
37 Cranswick K and Dosman D (2008) Eldercare: What We Know Today. Component of Statistics Canada Catalogue no. 11-008-X Canadian Social Trends.
38 Parkinson Society Canada (2003). Parkinson's: The Facts.
39 M et al (2001) Parkinsonism in Ontario: increased mortality compared to controls in a large cohort study. *Neurology*; 57:2278-2282.

In the U.S., the estimated contribution of environmental pollutants to the cost of pediatric disease is similarly enormous. In 2002, economic losses attributable to childhood lead exposures were estimated at $43.4 billion per year; $2.0 billion annually for pediatric asthma; $0.3 billion for childhood cancer; and $9.2 billion for neurobehavioral disorders. These estimates are considered low due to the use of conservative assumptions and exclusion of related costs to families or later complications of these health conditions in children and also because of the incomplete knowledge of the role of environmental contaminants in these health outcomes.[40] Indeed, an updated and expanded version of this analysis concludes that annual costs were $76.6 billion in 2008 for lead poisoning, prenatal methylmercury exposure, childhood cancer, asthma, intellectual disability, autism and attention deficit hyperactivity disorder.[41]

2.2 The Impact of Poverty

Also relevant to an overview of statistics on chronic disease in the aging Canadian population are measures of longevity and quality of life for people living in poverty. As the issue of poverty is central to the discussion that follows, two points are important to note here:

- Statistics Canada reports that for people living in poverty in Canada, they experience significantly poorer health and a significantly shorter life expectancy than their wealthier counterparts in a study that "indicates strong and consistent evidence of socio-economic disparities in health."[42,43]
- Poverty affects large numbers of people in Canada including 1 in every ten children; in First Nations communities, that number rises to one in every four children.[44]
- Using a definition of "relative poverty" developed by the OECD, this childhood poverty estimate rises to 15% of children in Canada.[45]

2.2 Chronic Disease and Care in Canada's Aging Population – Key Points

- Canada has an aging population (currently, 13 % are aged 65 and over, predicted to rise to 25% by 2036) with high prevalence and in many cases rising incidence of many chronic diseases.
- 80% of those over 65 have one chronic disease, and, of those, 70% have two or more chronic diseases.
- In addition, more and more children are experiencing chronic diseases, or conditions, such as obesity, that lead to chronic diseases.
- Low birth weight and preterm births are understood to be indicators of potential lifelong consequences (as discussed throughout this report) and incidence of preterm birth in Canada (excluding data from Ontario) has been rising steadily for 20 years.
- In Ontario, one in three people (of all ages) have one or more chronic diseases, and at least 60% of Ontario's health care costs are due to chronic diseases.
- In Canada, the prevalence of the most prominent chronic diseases is estimated to affect multi-millions of individuals and direct cost estimates are in the multi-billions of dollars, although indirect costs of family caregivers providing unpaid care are often unrecognized.
- The annual disease burden attributable to environmental exposures has been estimated from studying mortality, hospitalizations, patient-days spent in hospital, and low birth weight and serious congenital anomalies, for four major categories of diseases

40 Landrigan PJ et al (2002) Environmental Pollutants and Disease in American Children: Estimates of Morbidity, Mortality, and Costs for Lead Poisoning, Asthma, Cancer, and Developmental Disabilities. *Environmental Health Perspectives*; 110(7):721-728.

41 Trasande L and Liu Y (2011) Reducing the Staggering Costs of Environmental Disease in Children, Estimated at $76.6 Billion in 2008. *Health Affairs*; 30(5);863-870.

42 Statistics Canada (2009) Income disparities in health-adjusted life expectancy for Canadian adults, 1991 to 2001 Component of Statistics Canada Catalogue no. 82-003-X, *Health Reports*; 20(4):1-10.

43 See also: Fang R et al (2009) Disparities in chronic disease among Canada's low-income populations. *Preventing Chronic Disease*; 6(4):1-9.

44 Campaign 2000 (2009) 2009 Report Card on Child and Family Poverty in Canada: 1989 – 2009. www.campaign2000.ca

45 Organization for Economic Cooperation and Development (2008) Growing unequal: income distribution and poverty in OECD nations. Paris: Organization for Economic Cooperation and Development.

(respiratory, cardiovascular, cancer, and congenital affliction). Annual costs in Canada are conservatively estimated to be between $3.6 and $9.1 billion.

- There is strong and consistent evidence of socio-economic disparities in health, with significantly poorer health and shorter life expectancy for those living in poverty and large numbers of children living in poverty (1 in 10 children in Canada; 1 in 4 children in First Nations communities). Using the OECD definition of “relative poverty” the estimate for childhood poverty in Canada rises to 15% of children.

3.0 Understanding Environmental Exposures

3.1 Introduction

Weakness in understanding relationships between environmental exposure and health outcomes arises for multiple reasons that are explored further in Section 8.3. In general, the problem arises from, and is greatly compounded by, the reality of multiple exposures occurring across multiple media and often changing over time, by location, and lifestage such as in breastfeeding infants or other child-adult differences.

Environmental exposures can occur in air, water, food, soil, dust and from consumer products. In some cases, exposures to the same substance at varied levels can occur simultaneously across all media. For example, environmental lead contamination is measurable across air, water, soil, dust, etc., for reasons that will vary by location and circumstance. Of these, the most significant exposure medium for lead in young children is usually indoor dust,[46] whereas for adults lead exposure predominantly comes from food and drinking water.[47,48]

Environmental exposures can include chemicals (e.g., metals, industrial emissions, pesticides, components of consumer products, etc.) biological agents (mould, dust mites, etc.), and physical agents (e.g., radon, ionizing and ultraviolet radiation, etc.).

Chemical exposures originate from diverse uses of both naturally-occurring (e.g., metals, fossil fuels) and synthesized (e.g., petrochemicals) substances in diverse industrial processes, electricity generation, transportation and creation of consumer products.

While environmental exposures are typically or traditionally understood to result from pollution emissions or waste disposal across the production chain, or other forms of unwanted contamination (e.g., pesticide residues or persistent environmental pollutants in food), those arising from the use of consumer products are different. These exposures result from the

46 Dixon SL et al (2009) Exposure of U.S. children to residential dust lead, 1999-2004: II. The contribution of lead-contaminated dust to children's blood lead levels. *Environmental Health Perspectives*; 117(3): 468–74.

47 US Agency for Toxic Substances and Disease Registry (2007) Toxicological Profile for Lead. US Department Of Health And Human Services, Public Health Service, Washington, DC.

48 European Food Safety Authority (2010) *Scientific Opinion on Lead in Food*. European Food Safety Authority Journal; 8(4):1570.147 pp.

intentional use of substances in diverse products or packaging – across virtually all aspects of modern life. The fact that such products create chemical exposures is a consequence of their use in the product rather than as an externalized pollutant emission. For example, brominated flame retardants have been used in diverse products such as the foam in stuffed furniture and computer casings. They can be measured in wildlife in the remotest parts of the world even though they originate long distances away in areas of human population, largely from the breakdown of consumer products inside homes or other buildings.[49]

In commerce in Canada there are approximately 23,000 chemicals and substances in use and more than 500 active ingredients used in thousands of pesticide products, with several hundred new substances generated every year.[50] Industrial pollution is released to air, water and land (underground injection, on-site and off-site releases).[51] Added to the air pollution burden from these direct industrial sources is the large contribution from all forms of transportation, not only cars, buses, trains, trucks and planes but large vehicles used in diverse industrial sectors including most agricultural activity.

3.1.1 Air Pollution

For air pollution, of particular concern are the toxic and smog-forming air pollutants, the so-called "criteria air contaminants" (CACs). These include coarse, fine and ultra-fine particulate matter (PM), carbon monoxide, oxides of sulphur and nitrogen, ammonia and VOCs. Two of these – nitrogen oxides and VOCs – create ground level ozone (in the presence of sunlight), another main component of smog. Ultrafine particles, or $PM_{2.5}$ (particles with a diameter of 2.5 microns down to 1.0 micron), are created by chemical reactions in the air (between nitrogen oxides, sulphur dioxide and VOCs). The surface of these small particles is covered with a mixture of toxic substances including sulphates, nitrates, ammonium ions, elemental carbon, PAHs, metals, and additional toxic organic compounds.[52]

Although the CACs include a relatively small number of pollutants, they comprise the lion's share of the overall volume of air pollution emissions, with levels greatest in areas of high traffic volume, industrial activity, coal-fired electricity generation and residential wood fuel combustion, with smaller contributions from many other activities such as incineration and cooking meat.[53] Extremely large amounts of total PM also result from a range of open sources particularly agriculture tilling and road dust.

In contrast, additional toxic air pollutants, arising from the same range of sources noted above, are measured at much lower levels in the atmosphere although the number and diversity of such pollutants is much higher than the CACs. Despite these lower overall volumes compared to CACs, concerns remain since such chemicals tend to be toxic at very low exposure levels. For example, the incineration of municipal waste and open burning of waste are the two largest sources of human-induced dioxin and furan (highly toxic POPs) emissions in Canada.[54]

Air pollution is also a concern indoors with multiple sources arising largely from consumer products though biological allergens, radon, and products of combustion are also important. Many indoor sources of contaminant exposure, arising almost entirely from diverse consumer products,

49 De Wit CA et al (2010) Brominated flame retardants in the Arctic environment — trends and new candidates. *Science of the Total Environment*; 408:2885–2918.

50 Health Canada (2005) Assessing and Managing the Health Risks of Existing Substances Under the Renewed Canadian Environmental Protection Act, 1999 (CEPA 1999) It's Your Health fact sheet series.

51 Commission for Environmental Cooperation (2011) *Taking Stock – North American Pollutant Releases and Transfers*.

52 Wigle D (2003) *Child Health and the Environment*. Chapter 11 – Outdoor Air. Oxford University Press.

53 Environment Canada, National Pollutant Release Inventory Online Data Search. http://www.ec.gc.ca/pdb/websol/emissions/ap/ap_query_e.cfm

54 Environment Canada, National Pollutant Release Inventory Online Data Search: 2009 Dioxins and Furans (D/F) Emissions for Canada

are increasingly understood to partition into house dust. This dust can also be contaminated by substances tracked in from myriad sources outdoors.

3.1.2 Drinking Water, Food and Soil

Drinking water may contain trace levels of contaminants, including chemicals that are products of disinfection, industrial effluents and pharmaceutical residues. In certain localized circumstances there may be biological contamination such as in communities with inadequate water treatment facilities that are under boil-water advisories. Drinking water may also contain geological contaminants such as arsenic (depending on local circumstances) or lead from plumbing, again, depending on local and building-specific circumstances.

Food can be an exposure source for contaminants in many different ways that will vary by food type, packaging/storage (e.g., plastic containers, lining of cans), and even food preparation choices (e.g., using plastics in the microwave, or grilling/charring food at high heat). In general, testing of foods for contaminant levels such as pesticide residues, metals or POPs, finds lower levels on fresh, whole foods than on multi-ingredient processed foods, especially where these are higher in fat content.[55,56]

The fat content of food significantly influences the levels of lipophilic contaminants (i.e., those that bind to fats). Such substances are often of greatest concern as they tend to include those that persist and biomagnify in the environment. They are also often highly toxic. Several of these POPs have been banned for many years but still circulate in the environment (e.g., polychlorinated biphenyls (PCBs), OC pesticides, etc.). Brominated flame retardants such as PBDEs, (banned or severely restricted more recently in many countries), are similar to PCBs in terms of chemical structure, toxicity and environmental persistence. The primary exposure source for PBDEs is indoor dust, particularly for young children, but exposure via food is also important, both later in life and where food has a high fat content.[57]

Soil pollution is generally a function of local circumstances such as the industrial use of land or the local or regional fallout of pollutants to soil from industrial activity or transportation corridors. These contaminants can often stay bound to soil particles and thus remain in place for a long time after the original source is halted or removed. Other examples include contamination of soil with arsenic beneath decks or other structures built from CCA-treated wood (this use of arsenic was banned in Canada in 2004) or with lead around older homes, porches and other structures from the use of lead-bearing paint (progressively banned since the mid-1970s).

3.1.3 Consumer Products

Finally, as already noted for lead and PBDEs, indoor dust is increasingly understood to be a significant exposure medium, particularly for children. A recent literature review[58] summarizes an extensive evidence base that describes numerous reasons why house dust and PM in indoor air are of primary importance to a consideration of children's exposures to toxic substances. This review notes that more than 100 potentially toxic substances and allergens have been identified in house dust. Sources are both indoors, from multiple consumer products, and outdoors, including tracking in contaminated soil and dust on shoes, stroller or bicycle wheels, etc. Larger dust and soil particles

55 Marques A et al (2011) New tools to assess toxicity, bioaccessibility and uptake of chemical contaminants in meat and seafood. *Food Research International*; 44:510-522.

56 Tittlemier SA et al (2007) Dietary Exposure of Canadians to Perfluorinated Carboxylates and Perfluorooctane Sulfonate via Consumption of Meat, Fish, Fast Foods, and Food Items Prepared in Their Packaging. *Journal of Agricultural and Food Chemistry*; 55:3203-3210.

57 Wu N et al (2007) Human exposure to PBDEs: associations of PBDE body burdens with food consumption and house dust concentrations. *Environmental Science and Technology*; 41(5):1584–1589.

58 Roberts JW et al (2009) Monitoring and Reducing Exposure of Infants to Pollutants in House Dust. *Reviews of Environmental Contamination and Toxicology*; 201:1-39.

can adhere to skin, clothing and other objects and be ingested by children via mouthing behaviour. Smaller particles can become airborne and be inhaled. The concentration of pesticides and PAHs in house dust are much higher on inhalable and respirable particles than on larger particles. Airborne particles and dust also settle, contributing to contaminant-bearing house dust. As well, some contaminants such as phthalates are semi-volatile and are thus available on product surfaces as well as in dust and indoor air.[59]

The above-noted literature review concludes that, in addition to lead and PBDEs, house dust is a major in-home exposure source for pesticides,[60] PAHs, phthalates and other endocrine disrupting compounds (EDCs), arsenic, chromium, mould, endotoxin and bacteria. Studies also demonstrate that these contaminants further concentrate on cleaning tools such as brooms, dusters or mops, and in the contents of a vacuum cleaner and even dryer lint.[61,62]

3.2 The Uniqueness of Early Exposures

It is often said that a mother's body is a child's first environment. A fetus and breastfeeding infant will experience a wide range of exposures through the mother's body – either those substances that can cross the placenta or that may be present in breast milk.[63] Such exposures in the fetal environment or in breast milk can arise from a woman's current exposures or via mobilization of contaminants that have accumulated in her body over her lifetime such as persistent substances stored in fat tissues or lead stored in bones or teeth.[64,65] It is also often said that humans occupy the top of the food chain. However, that place is in fact occupied by our breast-fed infants.

There is also sturdy evidence demonstrating that infants and children are more highly exposed to chemicals and pollution in the indoor and outdoor environment, compared to adults. For example, in a review of multiple studies investigating PBDE sources and pathways, children were found to have much higher exposure to these toxic flame retardants, primarily from indoor dust, with breast fed infants the most highly exposed.[66] In another example, preliminary evidence using a toxicokinetic model estimates that exposure to bisphenol A in young children may be as much as 11 times higher than adults.[67]

Strong evidence demonstrates that children are far more vulnerable than adults to the adverse effects of exposures to toxic substances due to their greater sensitivity during developmental stages including the immaturity of their detoxification systems.[68,69,70] The time of fetal development is the most sensitive. Child-adult exposure differences arise for several reasons including:

- proportional body size and weight, (e.g., kilogram for kilogram children are exposed to higher levels of contaminants in food or air);
- metabolism and physiology (e.g., children are generally more efficient at absorbing contaminants in the gut, they breathe more rapidly and tend to breathe more through the mouth); and

59 Xu Y et al (2010) Predicting Residential Exposure to Phthalate Plasticizer Emitted from Vinyl Flooring: Sensitivity, Uncertainty, and Implications for Biomonitoring. *Environmental Health Perspectives*; 118:253–258.

60 See also: Stout DM et al (2009) American Healthy Homes Survey: A National Study of Residential Pesticides Measured from Floor Wipes. *Environmental Science and Technology*; 43:4294-4300.

61 Costner P et al (2005) *Sick of Dust: Chemicals in Common Products, A Needless Health Risk in Our Homes*. Safer Products Project, Clean Production Action.

62 Schecter A et al (2009) PBDEs in U.S. and German clothes dryer lint: A potential source of indoor contamination and exposure. *Chemosphere*; 75:623-628.

63 Solomon GM and Weiss PM (2002) Chemical contaminants in breast milk: Time trends and regional variability. *Environmental Health Perspectives;* 110(6):A339–47.

64 Gulson BL et al (1997) Pregnancy increases mobilization of lead from maternal skeleton. *Journal of Laboratory and Clinical Medicine;* 130(1):51–62.

65 Hu H et al (1995) The role of nutrition in mitigating environmental insults: Policy and ethical issues. *Environmental Health Perspectives;* 103(Suppl. 6):185–90.

66 Johnson-Restrepo B and Kannan K (2009) An assessment of sources and pathways of human exposure to polybrominated diphenyl ethers in the United States. *Chemosphere*; 76:542-548.

67 Edginton AN and Ritter L (2009) Predicting Plasma Concentrations of Bisphenol A in Children Younger Than 2 Years of Age after Typical Feeding Schedules, using a Physiologically Based Toxicokinetic Model. *Environmental Health Perspectives*; 117:645–652.

68 Landrigan PL et al (2004) Children's health and the environment: public health issues and challenges for risk assessment. *Environmental Health Perspectives;* 112:257-265.

69 Selevan, SG et al (2000) Identifying critical windows of exposure for children's health. *Environmental Health Perspectives;* 108:451-455.

70 The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment. Tórshavn, Faroe Islands, Thursday May 24, 2007. *Basic and Clinical Pharmacology and Toxicology;* 102:73-75.

- behaviour (e.g., crawling and hand-to-mouth activity).[71]

In addition, some children are genetically more susceptible to certain exposures or health concerns than others due to human genetic variability, or specific genetic polymorphisms. For example, susceptibility of some individuals to asthma and asthma triggers such as air pollution is well understood to have a genetic component.[72] Another example involves differences in leukemia risk associated with prenatal pesticide exposure. Children with leukemia were shown to carry specific genetic characteristics that altered the ability of their liver to metabolize foreign substances, including pesticides.[73,74]

3.3 Human Biomonitoring Confirms Widespread Exposure

Human biomonitoring is the direct measurement of chemical substances in human tissues such as blood, urine, breastmilk, or sometimes hair or fingernails. Population-wide biomonitoring studies have been conducted in the United States for over 10 years to measure various contaminants in the child and adult population (and much longer for the measurement of individual substances such as lead).

3.3.1 Biomonitoring in Canada

The Canadian government initiated a national biomonitoring program in 2007 as an expansion to the Canadian Health Measures Survey.[75] In Cycle One they took blood and urine samples from 5000 people from across Canada, aged 6 to 79 years, and analyzed for metals, phthalates, PCBs, brominated flame retardants (BFRs), OC pesticides, OP insecticide metabolites, phenoxyherbicides, cotinine, perfluorinated compounds and Bisphenol A (BPA). Cycle Two has expanded the age range from 3 to 79 years with some variations on what chemicals are tested for at various ages as well as the addition of more chemicals such as carbamate and pyrethrin pesticides, and some PAHs.[76]

In 2008, Statistics Canada released partial results from the survey reporting on mean blood concentrations for lead, mercury and cadmium in Canadians.[77] The survey found that less than 1% of Canadians have blood lead concentrations above the Health Canada guidance value of 10 µg/dl[78] (micrograms per decilitre) demonstrating a multi-year reduction of blood-lead levels coinciding with the removal of lead from multiple sources, particularly from gasoline. While this reduction is good news, it is noteworthy that average blood-lead levels remain more than 100 times higher than the pre-industrial norm,[79] (the above-noted guidance level is over 600 times higher) and thus reflect the continued reality of widespread environmental lead contamination.

Additional reporting of results from Cycle One indicate continual widespread exposure to BPA in the Canadian population and show a link between elevated blood lead levels and older housing

71 Cooper K and Vanderlinden L (2009) Pollution, Chemicals and Children's Health. In: *Environmental Challenges and Opportunities,* Chapter 8. Gore CD and Stoett, PJ (eds) Emond Montgomery (Toronto).

72 Vercelli D (2008) Discovering susceptibility genes for asthma and allergy. *Nature Reviews – Immunology*; 8(3):169-182.

73 Infante-Rivard C et al (1999) Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology;* 10:481-487.

74 Infante-Rivard C and Sinnett D (1999) Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia. *Lancet*; 354:1819.

75 Health Canada (2007) Biomonitoring of Environmental Chemicals in Canadian Health Measures Survey. www.hc-sc.gc.ca/ewh-semt/contaminants/health-measures-sante-eng.php

76 Personal communication with Doug Haines, Director, Chemicals Surveillance Bureau, Health Canada, March 2, 2010.

77 Wong SL and Lye EJD (2008) Lead, mercury and cadmium levels in Canadians, *Health Reports; 19(4):31-36.* Statistics Canada, Catalogue no. 82-003-XPE

78 Since the majority of scientific literature on lead reports blood-lead measures in micrograms per decilitre, the Canadian convention of metric nomenclature is not used in this report to describe blood-lead levels.

79 Flagel AR and Smith DR (1992) Lead levels in preindustrial humans. *New England Journal of Medicine*; 326(19):1293-1294.

stock (greater than 50 years old) with levels higher among those of lower socioeconomic status.[80] In looking at the raw data released from Cycle One, without further analysis provided by Health Canada or Statistics Canada, these population-wide biomonitoring results indicate widespread and very low-level exposure to most of the metals tested, (e.g., antimony, arsenic, cadmium, lead, mercury, nickel, etc.), several metabolites of OC and OP pesticides, as well as exposure to phthalates, PCBs, PBDEs, PFOS and pyrethrin pesticides.[81]

Health Canada is also funding biomonitoring within several national and targeted population studies. For example, the Maternal Infant Research on Environmental Chemicals (MIREC) study is following approximately 2,000 pregnant women and their children up to age six months. They are testing blood, urine, hair and breast milk for heavy metals, phthalates, PCBs, brominated flame retardants, OC pesticides, and BPA.[82] In addition to MIREC, the Northern Contaminants Program, established in 1991, continues to assess human exposure and health impacts, including via human biomonitoring, of contaminants in wildlife species important to traditional diets of northern Aboriginal peoples.[83] Several biomonitoring programs are also ongoing for targeted populations assessing exposure to lead, arsenic, chemicals in plastics, indoor exposures, and acrylamide.[84]

3.3.2 Biomonitoring in the United States

As of 2011, the United States is in its fifth cycle of population-based biomonitoring. Since beginning in 2001, the stated aims of this program are to: determine which chemicals get into Americans and at what concentrations; determine the prevalence of people with levels above known toxicity levels; establish reference ranges; assess the effectiveness of public health efforts to reduce exposures; determine which groups are vulnerable; track levels over time; and, set priorities for research.

As of 2009, the CDC issued four reports documenting their work in biomonitoring, popularly known as the First, Second, Third and Fourth Reports.

In the Third Report, published in 2005, of those Americans tested for 137 different chemicals or chemical metabolites, 100 percent had detectable levels of pesticide residues in their bodies. It is noteworthy in this context that children who eat organic food have been found to have lower pesticide body burdens than those eating a conventional diet.[85] Phthalates, chemicals found in many cosmetics (nail polish, shampoos), soft plastic toys and tubing were found in most people. Children routinely had higher levels of phthalate metabolites in their urine compared to the adults. PCBs were still commonly found though at levels showing the ongoing reduction of contamination since these substances were discontinued in the 1970s. Their persistence in the environment is apparent in these and most other biomonitoring results. Six percent of American women of child-bearing age were found to have levels of mercury in their blood at or above the tolerable intake level (known as the reference dose in the U.S.).[86] Closer investigation showed even higher numbers of women with elevated levels if they lived near coastlines or were from cultural backgrounds that value a diet high in fish content. Although continuing a multi-year downward trend, a significant proportion of American children still carried levels of lead in their blood above health levels of concern.[87]

80 Bushnik T et al (2010) Lead and bisphenol A concentrations in the Canadian population. *Health Reports;* 21(3):7-18. Statistics Canada Catalogue no. 82-003-XPE

81 Health Canada (2010) *Report on Human Biomonitoring of Environmental Chemicals in Canada. Results of the Canadian Health Measures Survey Cycle 1 (2007–2009)*.

82 Maternal Infant Research on Environmental Chemicals (MIREC) A National Profile of In Utero and Lactational Exposure to Environmental Contaminants. www.mirec-canada.ca/site/index.php

83 Indian and Northern Affairs Canada, Northern Contaminants Program: http://www.ainc-inac.gc.ca/nth/ct/ncp/index-eng.asp

84 Government of Canada (2009) Targetted Population Biomonitoring Initiatives: http://www.chemicalsubstanceschimiques.gc.ca/plan/surveil/bio-target_pop-ciblees-eng.php

85 Lu C et al (2006) Organic Diets Significantly Lower Children's Dietary Exposure to Organophosphorus Pesticides. *Environmental Health Perspectives*; 114(20):260-263.

86 Jones RL et al (2004) Blood Mercury Levels in Young Children and Childbearing-Aged Women in the United States, 1999-2002. *Morbidity and Mortality Weekly*; 53(43):1018-1020.

87 Centers for Disease Control and Prevention (2005) *Third National Report on Human Exposure to Environmental Chemicals*.

The Fourth Report, published in 2009, includes results for an additional 75 chemicals measured for the first time in the U.S. population.[88] Results reveal:

- There are detectable levels of 212 chemicals in the blood and urine of people in the U.S. These samples were taken from 2,400 people, and include the pesticide atrazine, the gas additive methyl *tert*-butyl ether (MTBE), the solvent benzene and BPA;
- There is evidence of widespread exposure to some common industrial chemicals. For example, PBDEs were found in nearly all participants, BPA, was found in more than 90% of the samples, and perfluorinated chemicals, a group which includes perfluorooctanoic acid (PFOA), used in the creation of non-stick cookware coatings, was detected at measurable levels in most people in the study;
- The percentage of blood lead levels in children aged 1 to 5 years has continued to decline since the late 1970s (as noted above);
- Presence of acrylamide, which was assessed for the first time, is extremely common in the U.S. population. Acrylamide is formed when foods containing carbohydrates are cooked at high temperatures and is also a byproduct of tobacco smoke;
- Mercury levels in blood increase with age for all groups with older women of childbearing age (40-49) having the highest total blood mercury levels;
- Perchlorate, which is used in the manufacturing of fireworks, explosives, flares and rocket propellant, was detected in the urine of all participants in the study;
- a high percentage of people had detectable levels of the gasoline additive methyl *tert*-butyl ether (MTBE); and,
- About 5% of the participants over age 20 had urinary cadmium levels near or at levels which may be associated with health risks.

Alongside these population-based studies, numerous smaller studies from around the world confirm that all people carry household, agricultural and industrial chemicals (or their metabolites) in their bodies; sometimes called the "body burden" of chemicals.[89,90,91,92]

The finding of toxic substances in blood and urine does not necessarily equate with health effects. Rather, it provides an indication of widespread exposure for different age groups and different circumstances, highlights the greater exposure of children, and provides an important source of information for understanding the potential health impacts of multiple chemical exposures.

3.4 Understanding Environmental Exposures – Key Points

- The reality of multiple exposures occurring across multiple media and often changing over time, by location, and by lifestage, creates challenges in understanding relationships between environmental exposures and health outcomes.
- Environmental exposures can occur in air, soil, dust, food, water, and consumer products, as well as simultaneously across all media.
- In Canada, there are approximately 23,000 chemicals in use, and exposure can result from pollution emissions from industrial processes, electricity generation, transportation, waste disposal and creation of consumer products, but also from the intentional use of diverse products and packaging across virtually all aspects of modern life.
- Outdoor air pollution containing primarily CACs, including coarse, fine and ultra-fine particulate matter (PM), carbon monoxide, oxides of sulphur and nitrogen, ammonia and VOCs, is greatest in areas of high traffic volume, industrial activity, coal-fired electricity

88 Centers for Disease Control and Prevention (2009) Fourth National Report on Human Exposure to Environmental Chemicals. www.cdc.gov/exposurereport/

89 Environmental Defence (2006) Polluted Children, *Toxic Nation: A Report on Pollution in Canadian Families*.

90 Environmental Defence (2005) *Toxic Nation: A Report on Pollution in Canadians*.

91 Environmental Working Group and Rachel's Network (2009) *Pollution in People: Cord Blood Contaminants in Minority Newborns*.

92 Gonzalez, S. 2009 Mind Disrupted. How Toxic Chemicals May Change How We Think and Who We Are. A Biomonitoring Project with Leaders of the Learning and Developmental Disabilities Initiative. http://www.minddisrupted.org/index.php

generation, and residential wood fuel combustion, with smaller contributions from many other activities.

- Lower volume, but more diverse outdoor air pollutants that are frequently more toxic at lower levels are emitted from similar sources e.g. the largest sources of dioxin and furan emissions in Canada are from incineration of municipal and medical waste.
- Soil pollution can result from legacy industrial site contamination or toxic metals use (e.g. lead in paint and gasoline; arsenic in wood preservative.
- Indoor air pollution arises largely from consumer products, which are increasingly understood to partition into house dust, as well as products of combustion, biological allergens, and radon.
- Drinking water may contain disinfection byproducts, industrial effluents and pharmaceutical residues, biological contamination, as well as geological contaminants such as arsenic, or lead used in plumbing.
- Food contamination depends on food type, processing, packaging, storage, and preparation methods, as well as fat content (lipophilic contaminants tend to be persistent and bioaccumulative, and are often highly toxic).
- Extensive evidence indicates that house dust contains more than 100 potentially toxic substances and allergens. House dust and PM in indoor air, from indoor and outdoor sources, are among the most important media for childhood exposures to lead, PBDEs, pesticides, PAHs, phthalates and other endocrine disrupting compounds (EDCs), arsenic, chromium, mould, endotoxin and bacteria.
- A mother's body is a child's first environment, with many toxicants able to cross the placenta and to be expressed in breast milk.
- Infants and children are more exposed to environmental contaminants than adults because of their relatively larger absorptive surface areas, more rapid breathing, higher rate of ingestion, hand to mouth exploratory behaviour, as well as rapidly developing, still immature organs and body systems, including detoxification systems.
- Some children are genetically more susceptible to environmental insults.
- Human biomonitoring has revealed multiple chemicals in blood, urine, breast milk, and sometimes hair, nails, and sweat both in large population-based studies in Canada and the U.S., as well as in several smaller studies. Humans of all ages, from newborns to those entering their 8th decade, have retained legacy substances such as lead, mercury, PBDEs, PCBs, and OC pesticides, as well as substances still being produced such as BPA, perfluorinated compounds, acrylamide and perchlorate.

4.0 The Multiple Determinants of Health (MDOH)

4.1 Introduction

The conceptual framework of the multiple determinants of health (MDOH) arises from an understanding that many complex and dynamic factors combine, and often interact, to influence individual and population health. It is an evolving framework that originates from wide-ranging health research efforts, largely based in Canada that culminated in the *Ottawa Charter for Health Promotion*, a document that arose from the First International Conference on Health Promotion, held in Ottawa in 1986.[93]

Ten years on, Health Canada provided one of the most commonly used lists of the multiple determinants, within the context of describing that agency's approach to population health.[94] This same list of determinants is illustrated in Figure 1, created by the WHO.

This framing remains useful and important but it can be limited in conveying the breadth of issues in the areas of the social determinants of health (SDOH) [95] and the environmental influences on health. Moreover, the application of the MDOH framework, in public health or the traditional health sciences, tends to focus either exclusively or dominantly on the influence of behavioural (diet, smoking, etc.) and biomedical (e.g., cholesterol levels, body weight, etc.) risk factors contributing to health or disease. [96]

While lifestyle factors – smoking, unhealthy eating and physical inactivity – are known to contribute directly and significantly to multiple chronic diseases, there is robust literature in Canada and around the world documenting the large and arguably more important influence of the SDOH as well as the crucial role of early child development (ECD)[97] in ensuring lifelong health.

93 Ottawa Charter for Health Promotion. First International Conference on Health Promotion, Ottawa, 21 November 1986 http://www.who.int/healthpromotion/conferences/previous/ottawa/en/index.html

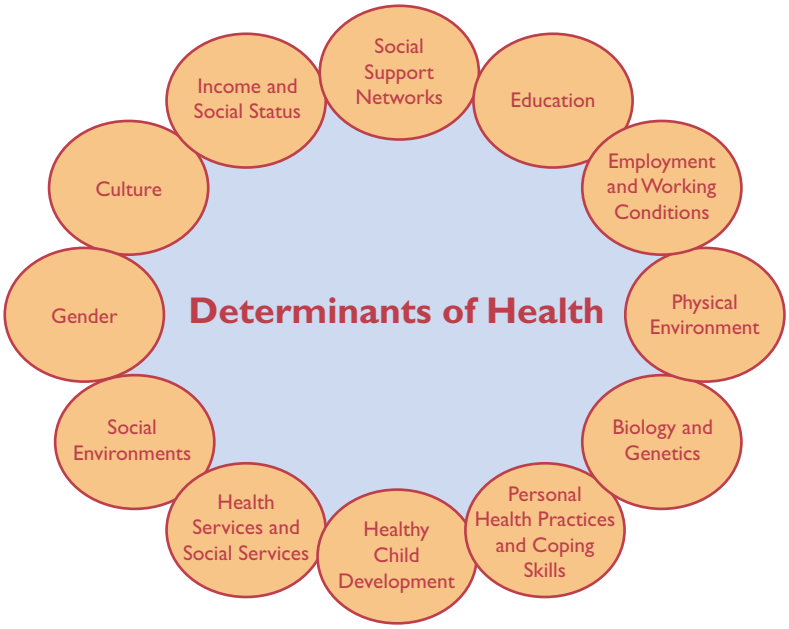
94 Health Canada. (1998) Taking action on population health: A position paper for health promotion and programs branch staff. Ottawa: Health Canada.

95 Raphael D (ed) (2009) Social Determinants of Health, Second Edition. Canadian Scholars' Press; Toronto.

96 Raphael D (2009) Escaping from the Phantom Zone: social determinants of health, public health units and public policy in Canada. *Health Promotion International*; 24(2): 193-198.

97 McCain M et al (2007) Early Years Study 2: Putting Science into Action, Council for Early Child Development.

Figure 1: Determinants of Health



Source: World Health Organization, undated.

At the same time, as reviewed in this report, there is increasing evidence of the role environmental factors, such as exposure to pollution and toxic chemicals, play in the development and/or exacerbation of many chronic diseases and conditions that is often incompletely recognized in the SDOH literature and is generally ignored in the ECD literature in Canada, though not in the U.S. (as discussed further below).

4.2 Behavioural and Biomedical Risk Factors for Chronic Disease

Varying frameworks exist to describe how chronic diseases result from many interacting causes. For example, the Public Health Agency of Canada describes the disease endpoints of cardiovascular disease, diabetes and several cancers as sharing common risk factors and conditions.[98] Risk factors are described as non-modifiable such as age, sex, level of education and genetics. Behavioural, or modifiable, risk factors include smoking, alcohol consumption, as well as exercise and eating habits. Intermediate conditions for chronic disease are also described in this framework including biomedical risk factors such as high blood pressure, high blood cholesterol, obesity or overweight, and high blood sugar. Social, cultural and environmental conditions round out the list of factors contributing to chronic disease. In a report framing the risk factors, determinants and prevention priorities for chronic disease in Ontario, the Ontario Chronic Disease Prevention Alliance characterizes behavioural and biomedical risk factors as "proximal" and the social, cultural and environmental factors as "distal" although the weight of each may vary with individuals and communities.[99]

Leaving aside the factors of social, cultural and environmental determinants, (discussed in detail below), the behavioural and biomedical risk factors have been well-studied in terms of their known contributions to chronic disease. For example, smoking is well understood to cause lung cancer. Cardiovascular disease and type 2 diabetes are commonly described as diet-related diseases or diseases of inflammation (e.g., as seen via biomarkers in blood tests indicating cellular or systemic inflammation and oxidative stress associated with obesity and/or a diet high in saturated fats and high glycemic carbohydrates). As well, strong evidence demonstrates associations between alcohol use (beyond moderate amounts) and several cancers. Lack of exercise is understood to contribute to overweight/obesity.

98 Public Health Agency of Canada website. Chronic Disease Risk Factors. http://www.phac-aspc.gc.ca/cd-mc/risk_factors-facteurs_risque-eng.php Accessed: November 2, 2009

99 Hayden E et al (2006) *Chronic Disease in Ontario and Canada: Determinants, Risk Factors and Prevention Priorities.* Report prepared for the Ontario Chronic Disease Prevention Alliance and the Ontario Public Health Association.

Tables 3 and 4 are adapted from the OCDPA report cited above and similar information from the Ontario Ministry of Health and Long Term Care. They summarize the existing knowledge base concerning how certain risk factors and intermediate conditions (or intermediaries) are common to many chronic diseases. Across these two tables, cardio-vascular disease, among the leading causes of death in Canada (see Table 2), is conspicuously associated with almost all of the risk factors and intermediate conditions noted in these tables. Type 2 diabetes, a condition that is rising rapidly in the Canadian population, is also frequently present across both tables. Absent from such a summary is low birth weight although it is known to be associated with many of these same later life chronic diseases, as discussed in Part 2.

Chronic disease prevention strategies rely upon the available evidence about associations with chronic disease and the behavioural and biomedical risk factors noted in Tables 3 and 4. Such strategies often give priority to addressing what are sometimes called the "big three" behavioural risk factors: unhealthy eating, physical inactivity and tobacco use/exposure. These priorities are grounded in solid evidence that these common, modifiable risk factors underlie the majority of chronic disease deaths at all ages, in men and women, and in all parts of the world. For example, a joint report[100] from the WHO and the Public Health Agency of Canada summarizes various predictions as to the proportion of specific health outcomes that could be prevented by addressing these three risk factors. They note that an estimated 90% of type 2 diabetes and 80% of coronary heart disease could be avoided with good nutrition, regular exercise, elimination of smoking and stress management. They also estimate that a daily diet high in vegetables and fruit could reduce about 20% of cancer incidence. The estimate for cancer prevention rises to 40% if all three risk factors are addressed.

The "big three" risk factors are clearly very important but they are not the entire story. Indeed, in describing these three risk factors as the cause of the vast majority of chronic disease worldwide, the WHO also underscores the need to address the "causes of the causes," notably poverty, as discussed further below.

4.3 The Social Determinants of Health (SDOH)

The social determinants of health (SDOH) are the economic, social and living conditions of daily life, for individuals, communities and political jurisdictions as a whole.[101] As such, the SDOH encompass most of the determinants illustrated in Figure 1. For example, the economic and social conditions of an individual or an entire community will profoundly influence:

- personal health practices and coping skills;
- the circumstances and degree to which healthy child development can occur;
- the access to and use of health services and social services;
- the nature and extent of social environments;
- the level of income and social status achieved;
- the existence and extent of social support networks;
- the level and quality of education obtained;
- the type and quality of employment and working conditions available;
- the physical environment in terms of quality and location of housing, proximity to pollution sources, and so on.

Not directly mentioned in Figure 1 are the most basic of human needs such as housing, water and food, the quality and availability of which will fundamentally influence health, and all of which can be profoundly influenced by the SDOH.

100 World Health Organization (2005) Preventing Chronic Diseases: A vital investment. World Health Organization and Public Health Agency of Canada. www.who.int/chp/chronic_disease_report/en/index.html

101 Raphael D (2009) Social Determinants of Health: An Overview of Key Issues and Themes. In: Raphael D (ed) *Social Determinants of Health, 2nd Ed.* Chapter One. Canadian Scholars' Press: Toronto.

Table 3: Risk Factors and Intermediate Conditions Known to be Associated with Chronic Disease	
Risk Factors (contributes to intermediate conditions)	**Health Outcomes**
Tobacco (high blood pressure)	• Chronic Obstructive Pulmonary Disease • Cancers of the stomach, larynx, pharynx, mouth, esophagus, lung, pancreas, bladder, kidney, colon • Cardiovascular disease
Unhealthy diet (high blood pressure) (high blood cholesterol) (overweight/obesity)	• Cardiovascular disease • Cancers of the lung, colon, breast and prostate • DiabetesT2 • Dementia (AD and vascular dementia)
Physical inactivity (high blood pressure) (high blood cholesterol) (overweight/obesity)	• Cancers of the colon and breast • Cardiovascular disease • DiabetesT2 or high blood sugar • Dementia (AD and vascular dementia)
Alcohol – excess use (high blood pressure) (overweight/obesity) (caveat: known to have a protective effect for CVD if consumed in moderation)	• Addictions • Major Depressive Episodes • Cancers of the stomach, mouth, pharynx, larynx, esophagus, liver, breast, colon • Liver cirrohosis • Cardiovascular disease • DiabetesT2 (depending on pattern of drinking)
Illicit Drug Use (often co-occurrence with tobacco and excess alcohol use)	• Hepatitis C • HIV • Liver Cirrhosis • Mental Disorders

Table 4: Intermediate Conditions Known to be Associated with Chronic Disease	
Intermediate Condition (contributes to additional intermediate conditions)	**Health Outcomes**
High blood pressure (high blood sugar)	• Cardiovascular disease • Renal disease • Diabetes T2 • Dementia (AD and vascular dementia)
Overweight/Obesity (high blood cholesterol) (high blood pressure)	• Cancers of the colon, breast and prostate • DiabetesT2 • Cardiovascular disease • Renal disease • Dementia (AD and vascular dementia and PD)
High blood sugar	• DiabetesT2 • Cardiovascular disease • Renal disease • Dementia (AD and vascular dementia)
High blood cholesterol	• Cardiovascular disease • Dementia (AD and vascular dementia)
Diabetes T2	• Stroke, Renal disease, amputations, blindness • Dementia (AD and vascular dementia)

Unlike behavioural choices or biomedical factors influencing health, which are individual in nature, the SDOH are the societal conditions that arise from fundamental decisions in a society about the organization and distribution of economic and social resources. These societal conditions will fundamentally influence for each individual in society their education, employment and income level, housing, social inclusion, etc. Educational attainment affects earning power, job satisfaction, and multiple aspects of health and well-being. Employment and income level determine the affordability and quality of housing, nutrition, access to and affordability of child care, etc. Indeed, across all of the co-dependent variables within the framework of the SDOH, these broader societal conditions will directly impact an individual's health, or their children's health. To cite one example, a large prospective study in the U.S. recently reported on finding associations between mortality, particularly from heart disease and cancer, and low socioeconomic status independent of lifestyle and dietary risk factors.[102] This study is illustrative of a considerable literature that demonstrates quantitatively and qualitatively that the SDOH are the primary determinants of both individual and population health,[103] and are of particular importance to children and their prospects for lifelong health.[104]

Recognition of this fact occurs in the final report of the Commission on Social Determinants of Health established by the WHO to "collect, collate, and synthesize global evidence on the social determinants of health and their impact on health inequity, and to make recommendations for action to address that inequity."[105] Although the result of ill health from impoverished living conditions is starkest among the poorest of the poor, the WHO Commission confirms that health and illness follows a social gradient worldwide: at all levels of income, the lower the socioeconomic position, the worse is a person's health. In documenting how these disparities flow from the current state of global economics and power distribution, this WHO report concludes that resulting health inequities can and must be put right, as a matter of social justice and indeed as an ethical imperative.

Canada's Chief Medical Officer of Health, in reviewing the literature on this topic, confirms the reality of this gradient in Canada in his 2008 Annual Report, [106] as does the Canadian Senate,[107] the City of Toronto,[108] and many others.[109,110] Canada's Chief Medical Officer of Health further confirms in his 2010 report[111] that the cumulative impact of socio-economic conditions on health outcomes is more apparent as people age and in his 2009 report notes that children living in poverty experience lifelong health consequences.[112]

The impact of the gradient associating income and health appears to be disproportionately felt by newcomers to Canada and is well known to be more significant in Aboriginal communities.[113] In describing the "healthy immigrant effect" Statistics Canada reports that the health of recent

102 Doubeni C et al (2010) Abstract PR-10: The association of neighborhood socioeconomic context and mortality in a large national cohort in the United States: The NIHA-ARP Diet and Health Study, *Cancer Prevention Research*, 2010;3(1 Suppl):PR-10.
103 Raphael D (ed) *Social Determinants of Health. 2nd Ed.* Canadian Scholars' Press: Toronto.
104 Raphael D (2011) Poverty in childhood and adverse health outcomes in adulthood. *Maturitas*: 69:22-26.
105 World Health Organization (2008) *Closing the gap in a generation: Health equity through action on the social determinants of health*. Geneva. Quoted from "Opening Note from the Chair."
106 Butler-Jones D et al (2008) *The Chief Public Health Officer's Report on the State of Public Health in Canada*. Ottawa.
107 Senate Subcommittee on Population Health (2008) *Canada Senate Subcommittee Reports: International Community's Approach to Population Health*. Senate of Canada, Ottawa.
108 Toronto Public Health (2008) *The Unequal City – Income and Health Inequalities in the City of Toronto*
109 Health Disparities Task Group of the Federal/Provincial/Territorial Advisory Committee on Population Health and Health Security (2004) *Reducing Health Disparities: Roles of the Health Sector: Discussion Paper*.
110 Kondo N et al (2009) Income inequality, mortality and self-rated health: meta-analysis of multi-level studies. *British Medical Journal*; 339:b4471.
111 Butler-Jones D (2010) *The Chief Public Health Officer's Report on the state of public health in Canada: Growing Older – Adding Life to Years*. Ottawa.
112 Butler-Jones D (2009) *The Chief Public Health Officer's Report on the state of public health in Canada: Growing Up Well – Priorities for a Healthy Future*. Ottawa.
113 Canadian Institute for Health Information (2004) Improving the Health of Canadians. http://secure.cihi.ca/cihiweb/products/IHC2004rev_e.pdf

immigrants to Canada often declines and that this change correlates with inactive leisure time, weight gain, low education and low household income.[114]

This gradient has been more extensively studied in urban populations, comprising approximately 66% of the population in Canada.[115] Moreover, most of these literature reviews recognize the multiple dimensions of socio-economic status, that is, beyond a single consideration of income levels. Researchers in Quebec seek to quantify and demonstrate socio-economic disparities in a more nuanced way, beyond income differences, by considering multiple indicators of material and social deprivation. In applying a "disparity index" tool, they confirm the well-researched impact of inequalities and social disparities on urban populations but they also demonstrate that these disparities extend to all geographic areas reflecting Canada's diversity.[116] Additional work seeks to apply a similar approach in Ontario.[117,118] In November of 2009, the president-elect of the Canadian Medical Association, Dr. Jeffrey Turnbull, stated that doctors in Canada must acknowledge poverty as the greatest predictor of an individual's health, that poverty and housing need to be considered human rights issues, and called upon doctors to advocate for strategies to reduce poverty and improve the health of society's most vulnerable citizens.[119]

This selection of recent reports and statements, mainly from public institutions in Canada, summarizes a very large amount of quantitative and qualitative evidence gathered by social scientists pointing to living conditions, i.e., the SDOH, as primary determinants of individual and population health. In summarizing this literature, these reports also recognize a central conclusion: as primary determinants, inattention to the SDOH can undermine individual behavioural choices to achieve better health, up to and including the ability to adopt such choices at all.

To augment Figure 1, social scientists posit a more comprehensive list of the SDOH[120] as follows:

- Aboriginal status
- early life/early child development
- education
- employment and working conditions
- food security
- gender
- health services
- housing/homelessness
- income and income distribution
- social inclusion/exclusion
- social safety net
- unemployment

Notably, Ontario's Chief Medical Officer of Health includes this broader perspective on the SDOH in her 2009 Annual Report.[121]

114 Ng E et al (2005) *Dynamics of Immigrants' Health in Canada: Evidence from the National Population Health Survey. Healthy today, healthy tomorrow?* Health Analysis and Measurement Group. Component of Statistics Canada - Catalogue no. 82-618-MWE 2005002

115 Canadian Institute for Health Information (2008) *Reducing Gaps in Health: A Focus on Socio-Economic Status in Urban Canada.*

116 Pampalon R et al (2009) A deprivation index for health planning in Canada. *Chronic Diseases in Canada;* 29(4):178-191.

117 Matern R et al (2009) *Developing a Deprivation Index: The Research Process*. Report for the Daily Bread Food Bank and the Caledon Institute of Social Policy.

118 Matern R et al (2009) *Testing the Validity of the Ontario Deprivation Index*. Report for the Daily Bread Food Bank and the Caledon Institute of Social Policy.

119 Duffy A (2009) Fix poverty, fix health, top MD says. CMA's president-elect tells homelessness forum doctors must serve community, not just patients, *Ottawa Citizen*, November 24, 2009.

120 Adapted from: Raphael D (ed) (2008).*Social Determinants of Health, 2nd Edition*. Toronto: Canadian Scholars' Press.

121 King A (2010) Public Health – Everyone's Business. 2009 Annual Report of the Chief Medical Officer of Health of Ontario to the Legislative Assembly of Ontario. http://www.health.gov.on.ca/en/public/publications/ministry_reports/cmoh_09/cmoh_09.pdf

4.4 Environmental Determinants of Health

Figure 1 is similarly limited in capturing the range and depth of factors and issues that can be considered among the environmental determinants of health. It notes the "physical environment" as a single determinant. Yet these words can encompass the entirety of outdoor and indoor circumstances of people's lives. As outlined in Section 3 above with respect to the breadth of possible environmental exposures, within the single notion of "physical environment" is the potential for multiple pollutant or hazardous chemical exposures. The quality of the physical environment is affected by activities occurring on a scale from individual to local to regional to global. Activities or circumstances that can influence environmental exposures can be broadly varied including:

- what people eat
- drinking water sources
- products used
- where people live and work
- the outdoor built environment and related land use planning
- agricultural or industrial activities
- energy production
- transportation
- waste disposal activities
- historical activities resulting in contaminated lands

Finally, access to, and the quality of, the natural environment, will vary according to land use practices and the varied circumstances of people's lives.

Where a common set of exposures are apparent, that is, those where most people would be exposed in generally the same way, these might include the impaired air quality during a regional smog advisory or indoor exposures that arise from consumer products such as fragrances in commonly used dish soap or shampoo. However, further generalization becomes difficult. In line with the wide variability in any definition of physical environment, there will be inherent differences in exposures for people living in different regions, in urban or rural settings, working in different occupations, etc. More fundamentally, environment is similar to income level or gender, in terms of being one of the cross-cutting determinants of health that interacts in many different ways with other determinants, particularly with many aspects of the SDOH (as discussed further in Section 5 below).

Embedded in the above long list of activities or circumstances that can create pollutant or hazardous chemical exposures are much broader environmental and societal issues that can significantly influence human health. For example, land use planning choices that result in our pervasively automobile-dependent lifestyle contribute to air pollution exposures, known to be harming human health,[122,123] but also contribute to climate change and a built environment that is widely recognized as contributing to sedentary lifestyles and related overweight/obesity.[124] As well, a rapidly expanding literature documents the combined impact of the increasingly mechanized, centralized and fossil-fuel dependent food production and marketing system in North America, and increasingly worldwide, as being a major contributor to both climate change and the glut of inexpensive sources of unhealthy food that are making a significant contribution to the current epidemic of overweight/obesity.[125,126,127, 128] This change in the food system has also altered food

122 Canadian Medical Association (2008) *No Breathing Room – National Illness Costs of Air Pollution*. Technical Report.
123 Ontario Medical Association (2005) *Illness cost of air pollution, 2005-2026 health and economic damage estimates*.
124 Ontario College of Family Physicians Environmental Health Committee (2005) *Report on Public Health and Urban Sprawl in Ontario: A review of the pertinent literature*.
125 Kingsolver B (2007) *Animal, Vegetable, Miracle – A Year of Food Life*. HarperCollins, New York.
126 Pollan M (2007) *The Omnivore's Dilemma – A Natural History of Four Meals*. The Penguin Press.
127 Shiva V (2008) *Soil Not Oil – Environmental Justice in an Age of Climate Crisis*. South End Press.
128 Nestle M (2006) Food marketing and childhood obesity – a matter of policy. *New England Journal of Medicine*; 354(24):2527-2529.

itself both in terms of the composition of individual foods and of the overall diet. The result has been a reduction in key micronutrients in food, changes in fat ratios (with many foods containing an unhealthy lowering of omega three fatty acids), and an increase in consumption of sodium, unhealthy fats, and high glycemic carbohydrates, all contributing to the obesity epidemic.[129,130,131]

Moreover, this obesity epidemic occurs disproportionately among low-income people with the apparent paradox of those in poverty experiencing both hunger and obesity. This phenomenon has additional environmental dimensions, including greater exposure to suspected obesogens in high fat foods (discussed in Section 3.3 below), and the unequal distribution of fast food restaurants and grocery stores, with the former at higher densities and the latter at lower densities in low income neighbourhoods.[132,133,134]

Across these four major issues – land use planning, automobile dependence, the built environment and the industrial food system – the issue of climate change looms large. Extensive research documents the anticipated impacts on human health of climate change itself including:

- impacts of catastrophic weather events, e.g., where these events may disrupt or damage sewage or water treatment infrastructure;
- anticipated increases in vector-borne disease and food-borne illness;
- extreme heat and poor air quality resulting in increased smog, increased levels of pollen and other aeroallergens, increased heat stress, increased heart and respiratory conditions and increased risk of premature death with greater risks for the elderly, the young and low-income people;
- greater UV radiation exposure if shelter is limited or unavailable;
- trauma from extreme events, especially for children; and,
- across many of these impacts, an expectation that First Nation communities reliant on traditional lifestyles will be disproportionately affected.[135]

The above impacts are well understood from climate change models developed internationally[136] and can be expected to occur in coming decades when an unprecedented one-quarter of the population of Canada will be senior citizens. More recently, a literature review focused on the interaction of chemical toxicants with climate change variables, found multiple reasons for concern including the likelihood that temperature increases will enhance the toxicity of contaminants as well as worsen air quality in already polluted regions, and that increased precipitation will increase surface deposition of airborne contaminants, and increase runoff of pesticides.[137]

> ***"The warming of the planet and the effects of extreme weather events can affect some of the most fundamental determinants of health: air, water, food, shelter, and freedom from disease."***
>
> ***World Health Organization Director-General***
> ***Dr. Margaret Chan***

129 See review in: Stein J et al (2008) *Environmental Threats to Healthy Aging: With a Closer Look at Alzheimer's and Parkinson's diseases*. Chapter 2 – The Changing Environment and Disease Patterns.
130 Davis DR et al (2006) Changes in U.S.DA Food Composition Data for 43 Garden Crops, 1950 to 1999. *Journal of the American College of Nutrition*; 23(6):669–682.
131 Gerrior S et al (2004). *Nutrient Content of the U.S. Food Supply, 1909-2000*. (Home Economics Research Report No. 56). U.S. Department of Agriculture, Center for Nutrition Policy and Promotion.
132 Dwyer JC (2005) *Hunger and Obesity in East Harlem: Environmental Influences on Urban Food Access*.
133 Horowitz CR et al (2004) Barriers to Buying Healthy Foods for People With Diabetes: Evidence of Environmental Disparities. *American Journal of Public Health*; 94:1549–1554.
134 Block J et al (2004) Fast Food, Race/Ethnicity, and Income: A Geographic Analysis. *American Journal of Preventative Medicine*; 27(3):211-217.
135 Health Canada (2008) *Human Health in a Changing Climate: A Canadian Assessment of Vulnerabilities and Adaptive Capacity*.
136 Intergovernmental Panel on Climate Change (2007) *Climate Change 2007, Fourth Assessment Report*.
137 Noyes PD et al (2009) The toxicology of climate change: Environmental contaminants in a warming world. *Environment International;* 35:971-986.

4.5 Multiple Determinants of Health – Key Points

- Many complex and dynamic factors combine, and often interact to influence individual and population health. The Multiple Determinants of Health (MDOH) framework is useful but it can be limited in conveying the breadth of issues in the areas of the social determinants of health and the environmental influences on health.
- Application of the model in public health or health sciences focuses heavily on behavioural and biomedical risk factors, whereas quantitative and qualitative evidence from around the world points to crucial influences of the social determinants of health (SDOH) and early child development (ECD).
- There is increasing evidence of the role environmental factors, such as exposure to pollution and toxic chemicals, play in the development and exacerbation of many chronic illnesses, but these have received limited attention in the SDOH and Canadian ECD literature.
- Behavioural or modifiable risk factors include smoking and alcohol consumption, as well as exercise and eating habits, which commonly overlap with intermediate conditions known to be associated with chronic disease. Such intermediate conditions can include biomedical risk factors such as high blood pressure, high blood cholesterol, obesity or overweight, and high blood sugar.
- Chronic disease prevention strategies give priority to addressing the "big three" behavioural risk factors: unhealthy eating, physical inactivity and tobacco use/exposure, which are not the entire story, given the primacy of basic human needs for food, water, and housing, and the SDOH, which are the economic, social, and living conditions of daily life.
- While behavioural choices or biomedical factors are individual, the SDOH are the societal conditions that arise from fundamental decisions in a society about the organization and distribution of economic and social resources.
- Although ill health is most prominent among the poorest of the poor, extensive evidence confirms that health and illness follow a social gradient worldwide: at all levels of income, the lower the socioeconomic position, the worse is a person's health. This gradient is also apparent in Canada with the most disproportionate affect on newcomers to Canada and Aboriginal communities.
- Inattention to the SDOH as primary determinants can undermine individual behavioural choices to achieve better health, including the ability to adopt such choices at all.
- Environmental determinants can encompass the entirety of indoor and outdoor circumstances of people's lives, with multiple media and routes of exposure to toxic substances.
- Physical environmental exposures can vary widely according to activities occurring on a scale from individual to local to regional to global.
- Environment is similar to income level or gender in being a cross-cutting determinant of health that interacts in many different ways with other determinants, especially the SDOH.
- Additional key environmental issues include land use planning choices that result in a pervasively automobile-dependent lifestyle that contributes to health-harming air pollution and climate change, a built environment that contributes to sedentary lifestyles and related overweight/obesity, and an increasingly mechanized, centralized and fossil fuel-dependent food production system that has not only changed the composition of food itself but is a major contributor to climate change and the glut of inexpensive sources of unhealthy food.
- Many severe health impacts of climate change are expected to occur in coming decades when an unprecedented one quarter of the population will be over age 65 and, if current

trends continue, the overwhelming majority if these seniors will be afflicted with at least one or more chronic diseases. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health- air, food, water and shelter.

5.0 Interactions Among Environmental Risk Factors and the SDOH

5.1 Introduction

Similar to the situation with the "big three" behavioural risk factors, (diet, exercise and smoking), the SDOH can also be of primary, underlying importance for environmental risk factors through increasing the likelihood and opportunities for exposure to harmful substances. An extensive literature exists in the United States,[138,139,140] and is emerging in Canada,[141,142,143,144,145,146] documenting the relationships between socio-economic status, environmental exposures and health. Internationally, it is well documented that in many nations, children living in extreme poverty, are likely to be disproportionately exposed to environmental hazards.[147,148] In addition to the known fact that children experience greater environmental exposures than adults,[149] poverty and related socio-economic conditions can magnify such hazards compounding existing health disparities. Several examples are discussed below.

138 Brown P (1995) Race, class and environmental health: A review and systematization of the literature. *Environmental Research;* 69:15-30.
139 Brulle R J and Pellow DN (2006) Environmental justice: Human health and environmental inequalities. *Annual Review of Public Health;* 27:10-24.
140 Lee C (2002) Environmental justice: building a unified vision of health and the environment. *Environmental Health Perspectives;* 110(*Suppl* 2):141-4.
141 Buzelli M (2008) *Environmental Justice in Canada: It Matters Where You Live*. Canadian Policy Research Network Research Report.
142 Chaudhuri N (1998) Child Health, Poverty and the Environment: The Canadian Context. *Canadian Journal of Public Health;* 89(*Suppl* 1):S26-30.
143 Finkelstein MM et al (2003) Relation between income, air pollution and mortality: a cohort study. *Canadian Medical Association Journal*; 169(5):397-402.
144 Gosline A and C Teelucksingh (2008) *Environmental Justice and Racism in Canada*, Emond Montgomery (Toronto).
145 Masuda JR et al (2008) Environmental health and vulnerable populations in Canada: mapping an integrated equity-focused research agenda. *The Canadian Geographer*; 52(4):427–450.
146 Wakefield SEL and Baxter J (2010) Linking Health Inequality and Environmental Justice: Articulating a Precautionary Framework for Research and Action. *Environmental Justice*; 3(3):95-102.
147 World Health Organization Regional Office for Europe and European Environment Agency (2002) *Children's health and the environment: A review of the evidence*.
148 World Health Organization (2006) *Preventing Disease Through Healthy Environments: Towards an estimate of the environmental burden of disease*.
149 Exceptions here would include adults who are occupationally exposed, for example to chemicals in industrial settings or to pesticides in agriculture or cosmetic uses of pesticides for lawn care.

5.2 Air Pollution

The relationship between low socioeconomic status and greater susceptibility to environmental exposures is apparent in several Canadian studies. In Hamilton, more pronounced impacts of air pollution were shown among poorer people, with higher pollution-related mortality.[150] Two Canadian studies show a similar pattern for multiple communities in the Great Lakes Basin[151] and Montreal[152] where areas with greater air pollution emissions correlate with higher rates of poverty. A similar relationship is reported between low household income and childhood respiratory health in a large cohort study in the United Kingdom.[153]

5.3 Housing, Schools and Play Areas

Where housing, schools, child care facilities or play areas are close to high-traffic roadways, greater exposure to traffic-related air pollutants will occur. Extensive literature in the U.S. documents the greater likelihood of communities with low-income and/or racial minorities to live near polluting industrial facilities or hazardous waste sites.[154] Canadian researchers are beginning to document similar situations in Canada such as the Africville community in Nova Scotia and multiple examples of environmental contamination problems affecting First Nations communities.[155,156]

The built environment is also known to contribute to sedentary lifestyles that can contribute to obesity for multiple reasons including automobile-dependent sprawl, a related lack of access to or efficiency of public transportation, or the tendency to avoid going outdoors if neighbourhoods are known or perceived to be unsafe.[157] Additional locational issues arise for low income communities in terms of access to stores selling healthy foods and the location of fast food outlets, in the context of the overall greater affordability of energy dense, lower quality food as discussed further in Section 10.2 with respect to risk factors for obesity.

Indoors, poor quality housing can increase exposure to mould, other biological allergens, pesticides, lead, asbestos and likely other contaminants as well.[158,159] Dampness can lead to an excess of dust mites and/or mould, it can provide a more welcome environment for cockroaches and rodents, and may also initiate chemical emissions from building materials and furnishings.[160,161] These circumstances can contribute to health effects directly, such as the contribution of dust mites and mould to asthma, but they may also contribute to increased use of pesticides and harsh cleaning products or both. Where poor quality housing, particularly apartments, has more frequent cockroach or other insect or rodent problems, it is likely to have more frequent applications of pesticides. Studies in the U.S. note that inner city, minority populations and are high-risk groups for indoor pesticide exposure.[162,163,164]

150 Finkelstein MM et al (2005) Environmental inequality and circulatory disease mortality gradients. *Journal of Epidemiology and Community Health*; 59:481–487.

151 PollutionWatch (2008) An Examination of Pollution and Poverty in the Great Lakes Basin. www.pollutionwatch.org Canadian Environmental Law Association and Environmental Defence.

152 Crouse DL et al (2009) Double burden of deprivation and high concentrations of ambient air pollution at the neighbourhood-scale in Montréal, Canada. *Social Science and Medicine*; 69:971-981.

153 Violato M et al (2009) The relationship between household income and childhood respiratory health in the United Kingdom. *Social Science and Medicine*; 69:955-963.

154 Bullard RD et al (2007) *Toxic Wastes and Race at Twenty, 1987 – 2007. Grassroots Struggles to Dismantle Environmental Racism in the United States*. A Report Prepared for the United Church of Christ Justice and Witness Ministries. United Church of Christ.

155 Gosine A and Teelucksingh C (2008) *Environmental Justice and Racism in Canada – An Introduction*. Emond Montgomery Publications.

156 Agyeman J et al (eds) (2009) *Speaking for Ourselves – Environmental Justice in Canada*. UBC Press.

157 Ontario College of Family Physicians (2005). *Report on Public Health and Urban Sprawl in Ontario: A review of the pertinent literature*. Environmental Health Committee OCFP.

158 Shaw M (2004) Housing and Public Health. *Annual Review of Public Health*; 25:397-418.

159 Bryant T (2009) Housing and Health: More Than Bricks and Mortar. In: *Social Determinants of Health, 2nd Edition*, Raphael D (ed) Chapter 15. Canadian Scholar's Press, Toronto.

160 Institute of Medicine (2000) *Clearing the Air: Asthma and Indoor Air Exposures*. Committee on the Assessment of Asthma and Indoor Air, Division of Health Promotion and Disease Prevention, Institute of Medicine, National Academy Press.

161 Institute of Medicine (2004) *Damp Indoor Spaces and Health*. Board on Health Promotion and Disease Prevention, Committee on Damp Indoor Spaces and Health, Institute of Medicine, National Academy Press.

162 Bradman A et al (2005) Association of Housing Disrepair Indicators with Cockroach and Rodent Infestations in a Cohort of Pregnant Latina Women and Their Children. *Environmental Health Perspectives*; 113:1795–1801.

163 Perera FP et al (2003) Effects of Transplacental Exposure to Environmental Pollutants on Birth Outcomes in a Multiethnic Population. *Environmental Health Perspectives;* 111(2) 201-205.

164 Landrigan PJ et al (1999) Pesticides and inner-city children: exposures, risks and prevention. *Environmental Health Perspectives*; 107(*Suppl* 3):431-437.

Lead in old paint remains a significant exposure hazard to children, pregnant women, and women who may become pregnant, in any dwellings built before 1978, particularly if housing is poorly maintained.[165] Whether it is negligent landlords, or parents who lack the resources or knowledge to contain or repair deteriorating paint, sub-standard housing, especially if there are dampness issues, will contribute to lead exposure among poorer children. However, regardless of socio-economic status, the legacy of lead paint means that renovation practices, including retrofits to achieve energy efficiency, if not carefully done, can create a serious lead hazard for young children and fetal exposure if pregnant women are present and involved in the renovation activities.[166]

In a 30-year retrospective analysis of population health and housing data in the U.S., consistent relationships were found between measures of housing quality, including measures of the surrounding community, and population health trends. Poor housing quality was related to higher levels of asthma, respiratory illness, obesity and diabetes, lead poisoning, among other health outcomes.[167,168]

5.4 Nutrition and Cultural Influences

Where nutrition is inadequate, as can occur under conditions of poverty or low income, in addition to the health risks thus created, children and the developing fetus are at greater risk for environmental exposures. Deficiencies in protein, calcium or iron can increase the absorption of toxic substances such as lead.[169,170] A child's digestive system absorbs more lead than an adult's (50% compared to 10%) while pregnant women will absorb lead at a rate similar to what occurs in children.[171] As in children, absorption of lead during pregnancy is greater where dietary calcium or iron is deficient with the potential result of even greater lead exposure during highly sensitive stages of fetal, infant and early childhood brain development.

The opposite appears to be the case as well. For example, good nutrition appears to offset the effects of methylmercury[172,173] and in Mexican mothers, calcium supplementation was associated with marked decrease in blood-lead levels, breastmilk lead levels and maternal bone resorption.[174] Indeed, nutritionists point out many areas where nutritional considerations are critical components in scientific investigations to understand the health risks of environmental pollutants.[175]

Aboriginal communities can be exposed to higher levels of food-borne contaminants than the general population, a situation that will be compounded by the influence of poverty, poor quality housing, compromised nutrition and other SDOH. The traditional Aboriginal diet of eating locally harvested fish and wildlife has cultural, spiritual and nutritional health significance. However, it also increases exposure to environmental contaminants particularly where the diet is high in fish or fish-eating mammals.[176] The same cultural importance of a diet high in fish, and corresponding opportunity for greater exposure to contaminants, can occur for coastal communities as well as within immigrant populations from Asia.

165 Centers for Disease Control and Prevention and U.S. Department of Housing and Urban Development (2006) *Healthy housing reference manual*. Chapter 5 – Indoor Air Pollutants, and Toxic Materials. Atlanta: U.S. Department of Health and Human Services.

166 Woodsworth A et al (2011) *Healthy Retrofits: The Case for Better Integration of Children's Environmental Health Protection into Energy Efficiency Programs*. Canadian Environmental Law Association.

167 Jacobs DE, et al (2009) The Relationship of Housing and Population Health: A 30-Year Retrospective Analysis. *Environmental Health Perspectives;* 117(4)597-604.

168 See also: World Health Organization Regional Office for Europe (2011) *Environmental burden of disease associated with inadequate housing - Methods for quantifying health impacts of selected housing risks in the WHO European Region*. Braubach M et al (eds).

169 Lanphear BP et al (2002) Environmental lead exposure during early childhood, *Journal of Pediatrics*; 140(1):40-47.

170 Mushak P and Crocetti AF (1996) Lead & Nutrition: Part II. Some potential impacts of lead-nutrient interactions in U.S. populations at risk. *Nutrition Today;* 31:115-122.

171 Wigle D (2003) *Child Health and the Environment*. Chapter 4 – Metals: Lead. Oxford University Press.

172 Clarkson TW and Strain JJ (2003) Nutritional factors may modify the toxic action of methyl mercury in fish-eating populations. *Journal of Nutrition*; 133(5 *Suppl* 1):1539S-43S.

173 Passos CJ et al (2003) Eating tropical fruit reduces mercury exposure from fish consumption in the Brazilian Amazon. *Environmental Research*; 93(2):123-30.

174 Hernandez-Avila M et al (2003) Dietary calcium supplements to lower blood lead levels in lactating women : a randomized placebo-controlled trial. *Epidemiology;* 14(2):206-212.

175 Hennig B et al (2007) Using Nutrition for Intervention and Prevention against Environmental Chemical Toxicity and Associated Diseases. *Environmental Health Perspectives;* 115(4)493-495.

176 Indian and Northern Affairs Canada (2003) *Human Health: Canadian Arctic Contaminants Assessment Report II*. Northern Contaminants Program.

5.5 Smoking

Exposure to ETS is a well-known indoor health hazard and smoking prevalence is twice as high among the lowest income Canadians compared to those in the highest income bracket.[177] Although annual reporting from the Canadian Tobacco Use Monitoring Study (CTUMS)[178] shows an overall downward trend in smoking across most age groups, the federal Ministerial Advisory Council on Tobacco Control stated in 2006 that the correlation between smoking and lower income and educational attainment was likely to continue to increase.[179] Whether these smokers contribute ETS exposure to their families is not entirely clear. The CTUMS data note a particularly sharp drop in the percentage of children exposed at home to ETS, age 0 to 11 years with a drop from 26% in 1999 to 6% in 2008 (for Canada as a whole; individual provincial numbers vary).

The overly simplistic notion of smoking being an individual behavioural choice is worth noting in a discussion of interrelationships between environmental and social factors. While the role of addiction is crucial, so too is the reality of smoking as a coping behaviour to address stressful circumstances that are more common among those living in poverty. Marketing and media also appear to play a role. While cigarette marketing has been progressively curtailed due to health concerns, strong evidence indicates that smoking in movies increases adolescent smoking initiation.[180] This effect was shown to be very large with over 50% of smoking initiation in the 10–14-year-olds that were studied being attributed to seeing smoking in movies compared to a level of about 35% accounted for by the effect of traditional cigarette advertising and promotion.

5.6 Quality and Age of Consumer Products

Many of the early environmental exposures of concern in this review originate in consumer products. Whether they are legacy issues like lead in old paint, PCBs used in products over forty years ago, banned pesticides that continue to circulate in the environment, recently banned flame retardants, or ongoing exposures to many different chemicals released from products, it is reasonable to assume that greater exposure occurs among low income individuals and families. The reasons for greater lead exposure from old paint under conditions of poverty are noted above.

Limited but increasing research demonstrates this assumption about greater exposure from products[181,182] under conditions of poverty but it is plausible for two reasons. First is the greater likelihood that inexpensive goods will be of lower quality and contain synthetic and potentially toxic substances. For example, an inexpensive vinyl shower curtain releases phthalates, especially when it is new, and needs to be replaced more often than a more expensive cloth curtain that does not release phthalates. Second is the likelihood that low-income people will use consumer products for a longer time either from the time of purchase or as second-hand items. For example, older electronics and furniture will contain now-banned BFRs. Where furniture covers are old and torn, with foam exposed, or if a piece of foam is used for a bed instead of a more expensive mattress, these items will shed more flame retardants to housedust than foam products that are newer or where the foam remains covered.

Where housing is sub-standard, it can be more difficult to keep clean, particularly to control dust. Older carpets are known to contain much higher levels of dust, and the related contaminant

177 Physicians for a Smoke-Free Canada (2005) Smoking in Canada – A statistical snapshot of smokers in Canada.
178 Health Canada, Canadian Tobacco Use Monitoring Survey. Overview of Historical Data 1999-2008: http://www.hc-sc.gc.ca/hc-ps/tobac-tabac/research-recherche/stat/_ctums-esutc_2008/ann-histo-eng.php#tab7
179 Ministerial Advisory Council on Tobacco Control: Biennial Report, 2004-2006. http://www.hc-sc.gc.ca/hc-ps/pubs/tobac-tabac/2006-mac-ccm/index-eng.php
180 Charlesworth A and Glantz SA (2005) Smoking in the Movies Increases Adolescent Smoking: A Review. *Pediatrics*; 116(6):1615-1628.
181 Roberts JW et al (2009) Monitoring and Reducing Exposure of Infants to Pollutants in House Dust. *Reviews of Environmental Contamination and Toxicology*; 201:1-39.
182 Zota AR et al (2010) Are PBDEs an environmental equity concern? Exposure disparities by socioeconomic status. Environmental Science and Technology; 44(15):5691-5692.

burden, than new carpets, 400 times as much dust and dirt than on the floor in the same home.[183] Access to a high quality vacuum cleaner will also be limited for those on low income.

For those who rely on food banks occasionally or regularly, greater consumption of canned foods will result in greater exposure to Bisphenol A from can linings. Plastic utensils and containers are less expensive and can likewise contribute to greater exposure to phthalates or bisphenol A if they are used more often than glass, ceramic or stainless steel.

5.7 Interacting Environmental and Social Risk factors – Key Points

- The SDOH can be of primary underlying importance for environmental risk factors, through increasing the likelihood of exposure to harmful substances, with poverty and related socio-economic conditions magnifying the already increased vulnerability of children compared to adults.
- There is evidence of more pronounced impacts of air pollution among poorer people, with higher pollution-related hospitalization and mortality rates.
- There is greater likelihood of communities with low income and/or racial minorities to live near polluting industrial facilities, hazardous waste sites, or high traffic corridors.
- Poor quality housing can increase exposure to mould, other biological allergens, pesticides, lead, asbestos, and likely other contaminants, and a U.S. 30-year retrospective analysis of population health and housing found that poor housing quality was related to higher levels of asthma, respiratory illness, obesity, diabetes, and lead poisoning, among other adverse health outcomes.
- When nutrition is inadequate, children and the developing fetus are at greater risk for environmental exposures. Deficiencies in protein, calcium or iron can enhance absorption of toxic substances such as lead.
- Cultural, as well as economic influences, affect intake of food-borne contaminants such as mercury and lipophillic POPs in fish; this occurs more often among Aboriginals, coastal community residents, and immigrant populations from Asia.
- Combining both locational and nutrition issues, low income communities can also tend to have limited access to stores selling good quality food, greater access to fast food outlets, and an overall tendency to consume lower quality, energy dense foods due to greater affordability.
- Smoking prevalence is twice as high among lowest income Canadians compared to the highest, but the Canadian Tobacco Use Monitoring Study shows a downward trend in most age groups, particularly in the percentage of children exposed at home to ETS.
- Many early environmental exposures of concern originate in consumer products. These can include legacy components such as lead, PCBs, banned pesticides and flame retardants and newer components such as phthalates and BPA in plastics. These and many other contaminants are known to partition to house dust and can be at very high levels in older carpets. Such product-based indoor exposures are plausibly higher in the poor because of longer use of lower quality or second-hand goods, including older dust-laden carpets, and greater consumption of canned food with bisphenol A-containing can liners. Exposure to lipophilic toxic substances will also be higher among those consuming a high fat diet.

183 Roberts JW and Dickey P (1995) Exposure of children to pollutants in house dust and indoor air. *Reviews of Environmental Contamination and Toxicology*; 143:59-78.

Photo: Sharon Pruitt (www.flickr.com/photos/pinksherbet)

6.0 Early Child Development

Groundbreaking work has occurred in Canada to synthesize evidence and improve understanding about the importance to lifelong health of experiences in the early years. Like the term "physical environment" in Figure 1, the term "early child development" (ECD) is another area that encompasses a complex set of variables that interact with each other and with other determinants to influence lifelong health. The *Early Years Study*, published in 1999 undertook a multi-disciplinary review of the evidence about the relationships among early brain and child development, and learning, behaviour, and health.[184] The report provides sturdy evidence about the importance of the early years (from birth to age six) in establishing the foundation for lifelong health. Ten years on, more evidence confirms and deepens this understanding about these multiple interacting factors.[185,186] Early experiences affect how the structure of the brain develops, the development of emotional and social temperament and coping skills, abilities with language and literacy, perception and cognition, and lifelong attitudes and capacities for both physical activity and psychological health.

Not only does this experience-based brain development affect lifelong health, fundamental aspects of brain development happen only once, in early childhood, and are thus of paramount importance. Like the literature about the SDOH, the literature on ECD confirms a strong correlation between disadvantaged conditions in childhood and multiple aspects of poorer health later in life,[187] including likely permanent adverse effects on brain function.[188] Both fields of study underlie the recommendations by Ontario's Special Advisor on Early Learning for full-day learning for 4- and 5-year olds in Ontario within the context of school-centred community programs staffed by

184 McCain MN and Mustard JF (1999) *Early Years Study Final Report – Reversing the Real Brain Drain*. April, 1999.
185 McCain MN et al (2007) *Early Years Study 2 – Putting Science Into Action*.
186 National Scientific Council on the Developing Child (2007) *The Science of Early Childhood Development: Closing the gap between what we know and what we do*. Center on the Developing Child at Harvard University, Cambridge MA.
187 Irwin LG et al (2007). *Early Child Development: A Powerful Equalizer*. Final Report of the World Health Organization's Commission on the Social Determinants of Health. Geneva: World Health Organization.
188 See for example: Kishiyama MM et al (2009) Socioeconomic Disparities Affect Prefrontal Function in Children. *Journal of Cognitive Neuroscience;* 2196):1106-1115.

teams of teachers and early childhood educators and with priority given to low-income areas as part of Ontario's Poverty Reduction Strategy.[189]

Both of the Early Years Studies, and the policy and practice changes they continue to stimulate, including the recommendations of Ontario's Special Advisor on Early Learning, have stressed the importance of ECD in economic terms. They point to long-term economic consequences of thwarted child development in terms of loss of human capital, poor health and inadequate community services. The solutions offered involve the need for collective problem-solving and inter-professional work across many disciplines, supported by a solid and compelling foundation in the neuroscientific evidence. It is ironic therefore that strikingly absent from this evidence review, in these seminal Canadian reports, is consideration of the evidence about the developmental neurotoxicity of environmental contaminants, particularly evidence concerning risks of fetal exposure to developmental neurotoxicants. Nor is this evidence considered in other key Canadian reports that further underscore the critical importance of early child development to a healthy economy or averting later social problems.[190,191,192,193]

In contrast, the evidence linking environmental contaminants to brain development is included in several reports prepared by the National Scientific Council on the Developing Child based at Harvard University. Reference is made to the need for continuous updating and enforcement of environmental protection policies to reduce prenatal and early childhood exposures and three detailed reviews address the available evidence concerning early exposures to environmental contaminants and impacts on brain development.[194,195,196] This evidence is briefly summarized in Section 11.6 below. The fact that the otherwise exemplary and influential Canadian studies on this topic do not consider this evidence illustrates a valuable reason for the collaboration behind this report; to review the evidence of environmental contributions to chronic diseases, and to put it into necessary context.

Some recognition of the potential for environmental contaminants to affect brain development is provided in the pediatric and family practice recommendations for physicians in Ontario.[197] However, although physicians are referred to Motherisk (at Sick Children's Hospital in Toronto) and to CPCHE's educational materials (i.e., reference to the *Playing it Safe* brochure[198]) the detailed recommendations for actual prenatal and postnatal care by physicians do not include recognition of the potential for toxic exposures other than in the workplace as a consideration under "other" factors.

Finally, regardless of whether environmental factors are included, sturdy evidence exists, and is reviewed in the U.S. and Canadian reports discussed above, demonstrating multiple links between ECD and the later development of chronic disease. These links often directly overlap with the evidence about the strong associations between the SDOH and the impact of poverty, parenting, etc., on ECD.

6.1 Early Child Development – Key Points

- Early experiences affect how the structure of the brain fundamentally develops in early childhood, the evolution of emotional and social temperament and coping skills, abilities

189 Pascal R (2009) *With Our Best Future in Mind - Implementing Early Learning in Ontario*. Report to the Premier by the Special Advisor on Early Learning.
190 Canadian Council on Learning (2007) *State of Learning in Canada, No Time for Complacency*. Report on Learning in Canada 07.
191 Canadian Council on Learning (2010) *State of Learning in Canada: A Year in Review*.
192 Mustard, J. F. (2006). *Early Child Development and Experience-based Brain Development: The Scientific Underpinnings of the Importance of Early Child Development in a Globalized World*. Washington, DC: Brookings Institute.
193 Best Start Expert Panel on Early Learning (2007) *Early Learning for Every Child Today: A framework for Ontario early childhood settings*.
194 National Scientific Council on the Developing Child (2006) *Early Exposure to Toxic Substances Damages Brain Architecture*. Working Paper #4. Center on the Developing Child, Harvard University.
195 National Scientific Council on the Developing Child, National Forum on Early Childhood Policy and Programs (2010) *The Foundations of Lifelong Health are Built in Early Childhood*. Center on the Developing Child, Harvard University.
196 National Scientific Council on the Developing Child (2007) *The Science of Early Childhood Development: Closing the Gap Between What We Know and What We Do*. Center on the Developing Child, Harvard University.
197 Ontario College of Family Physicians (2007) *Improving the odds: Healthy Child Development. Focus on the Early Years: Neuroscience and Implications for Clinical Practice*. TOOLKIT: Interdisciplinary MAINPRO CME for Family Physicians and other Primary Healthcare Providers, 4th Edition, 2007, Updated and Revised.
198 Canadian Partnership for Children's Health and Environment (2005) *Playing it Safe: Childproofing for Environmental Health*.

with language and literacy, perception and cognition, and lifelong attitudes and capacities for both physical activity and psychological health.

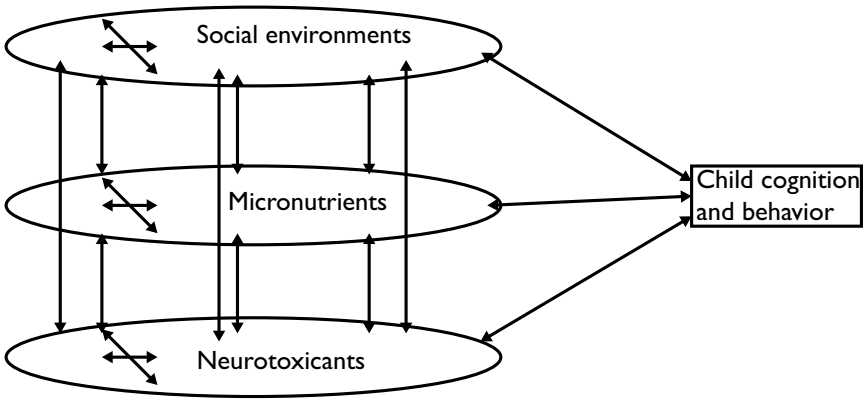
- Literature on ECD confirms a strong correlation between disadvantaged conditions in childhood and multiple aspects of poorer health later in life.
- There are long-term economic consequences of thwarted child development in terms of loss of human capital, poor health and inadequate community services.
- There is a striking absence from the Canadian ECD literature of consideration of the developmental neurotoxicity of environmental contaminants.
- The fact that the otherwise exemplary and influential Canadian studies on this topic do not consider the evidence about the developmental neurotoxicity of environmental exposures, particularly the greater vulnerability *in utero*, illustrates a valuable reason for the collaboration behind this report; to review the evidence of environmental contributions to chronic diseases, and to put it into necessary context.

7.0 Multiple Inter-relationships

Across the examples discussed herein, there are unlikely to be simple two-way relationships between, for example, a single toxic substance like lead and a single nutritional deficiency such as insufficient calcium, or, between lead in old paint and poor quality housing. Indeed, the notion of a single cause disrupting complex biological systems originates from the germ theory of disease in public health (e.g., a single micro-organism in drinking water causing a cholera epidemic). It has given rise to the approach of identifying multiple but individual (i.e., separate) risk factors. This approach is a useful means of identifying multiple risk factors but the research response tends to focus on individual pieces of the puzzle rather than the causal puzzle itself.[199] The resulting reductionist approach of enumerating, researching and attempting to reduce individual risk factors does not necessarily help in explaining crucial aspects about how they can interact.

One model for describing these relationships comes from a multi-disciplinary team of researchers, seeking to integrate the separate literatures on the impact of neurotoxicants, nutrients, and social environments. They devised the model reproduced in Figure 2 to illustrate the potential for interactions and effects on child cognition and behavior.[200] Each of these disciplines has amassed considerable studies showing relationships between adverse situations in each of these three domains (i.e., exposure to neurotoxic agents, micronutrient deficiency, and impoverished social environments) and negative impacts on child cognition and behaviour. As well, as Figure 2 illustrates, there can be multiple factors occurring and interacting within each domain as well as across two or all three. The relative importance of each can vary by circumstance and the authors chose not to indicate a hierarchy. Where all three are acting together, the three-tier model collapses to a single-tier where all three domains contribute to a child's cumulative risk.

Figure 2: Model of inter-relationships across domains and child outcomes



Such understanding of the individual and combined effects of toxic substances, social environments and nutrition is hampered by large gaps in knowledge about the exposure circumstances and potential health impacts of the myriad toxic substances to which children are exposed as well as the potential for interactions among these substances.

7.1 Complexity of Inter-relationships – Key Points

- There is a tendency for research to be reductionist in focusing on multiple but separate environmental risk factors for chronic disease, i.e. individual pieces of the puzzle, rather than the causal puzzle itself.

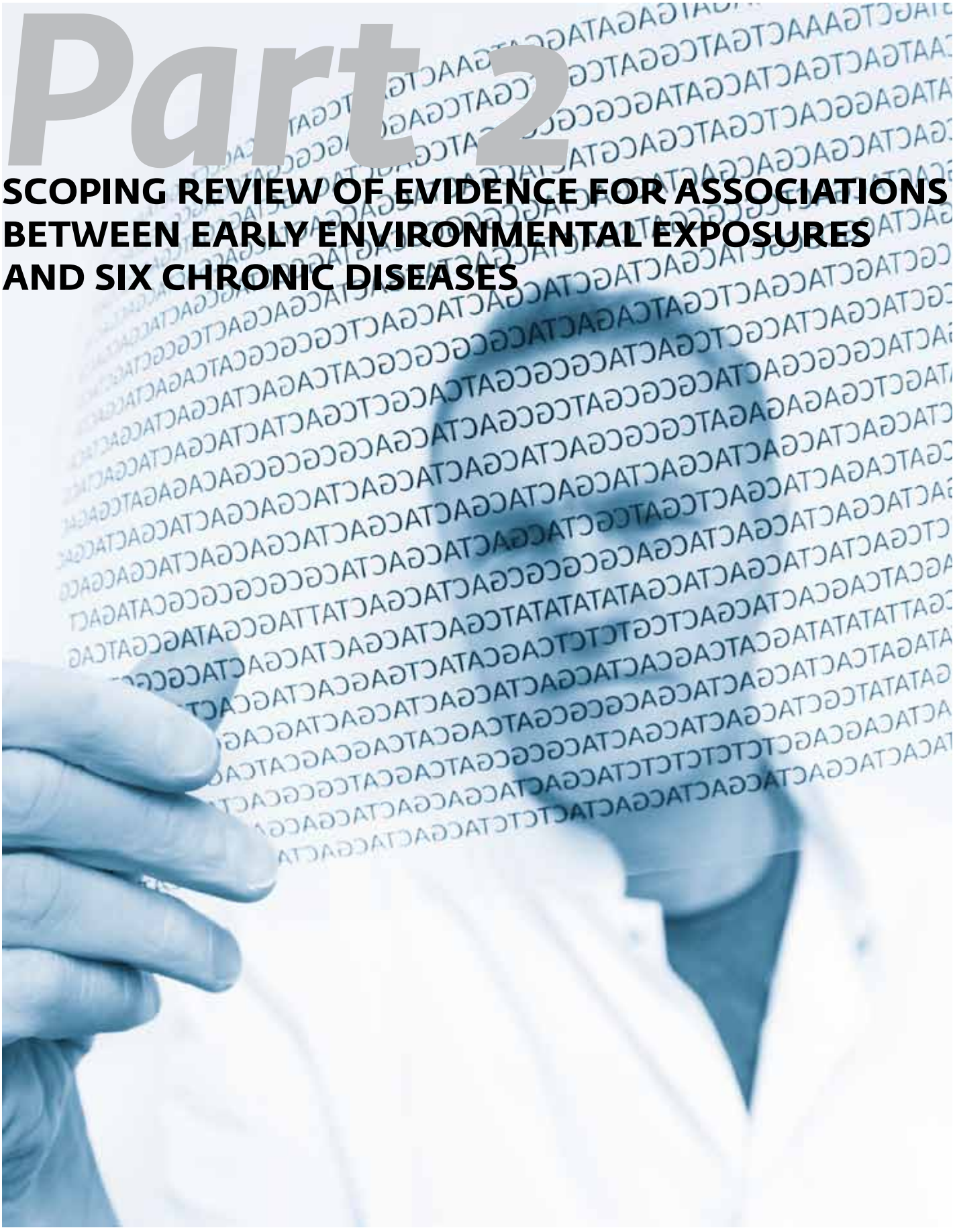
199 Gee D (2008) Establishing Evidence for Early Action: the Prevention of Reproductive and Developmental Harm. MiniReview in *Basic and Clinical Pharmacology and Toxicology;* 102: 257-266.

200 Hubbs-Tait L et al (2005) Neurotoxicants, Micronutrients and Social Environments: Individual and Combined Effects on Children's Development. *Psychological Science in the Public Interest*; 6(3):57-121.

- Understanding of the individual and combined effects of the domains of toxic substances, social environments, and nutrition is helped by recognition of how multiple factors can occur and interact within each domain as well as across two or all three, and that the relative importance of each can vary by circumstance. Understanding is hampered by large knowledge gaps about the exposure circumstances and potential health impacts of the many toxic substances to which children are exposed, as well as the potential for their interaction.

Part 2

SCOPING REVIEW OF EVIDENCE FOR ASSOCIATIONS BETWEEN EARLY ENVIRONMENTAL EXPOSURES AND SIX CHRONIC DISEASES



8.0 Introduction and Key Issues

The scientific evidence necessary to understand the contribution of environmental exposures to chronic diseases is often highly complex and fraught with uncertainty or information gaps. Even where evidence about health impacts is strong, such as for well-understood pollutants like lead or POPs, clear evidence of causal links to human health impacts is rarely available. There is also the challenge of sifting through the published studies for quality evidence. Good data about specific exposure circumstances are particularly lacking. Yet, multiple exposures continue in the face of high stakes risks. Or, as one author notes, in reference to the increasingly strong evidence about human-induced climate change, "the science is not settled, but it is unsettling."[201]

Recalling from the discussion in Sections 1 and 3 about project scope and the broad range of possible exposures, the evidence review about links to chronic disease is similarly broad spanning the breadth of human developmental changes from preconception to the end of adolescence. At issue is the potential for environmental exposures to affect these developmental stages and thus contribute to a wide range of chronic diseases or health conditions.

Within and in addition to the evidence about environmental risks to children's health that CPCHE has focused on for ten years, existing and emerging evidence points to an environmental contribution in the etiology of the following chronic diseases and conditions:

- cardiovascular disease
- Type 2 diabetes
- impacts on the brain, including Alzheimer's disease and Parkinson's disease
- several types of cancer, and
- asthma.

Three additional and overlapping issues are also relevant to a discussion of environmental factors in chronic disease including obesity, disruption or change to the immune and endocrine systems and environmental sensitivities, including multiple chemical sensitivities.

201 Friedman T (2008) *Hot, Flat and Crowded: Why we need a green revolution – and how it can renew America*. Farrar, Straus and Giroux.

8.1 The Developmental Origins of Health and Disease

Much of the contextual information provided in Part One of this report concerns the multi-dimensional nature of factors that contribute to chronic diseases, including the need to recognize that environmental exposures, particularly during periods of heightened vulnerability in early life, are part of that broader context.

The scientific evidence about how early environmental exposures affect children's health or contribute to later chronic disease sits within a broader framework referred to as the Developmental Origins of Health and Disease (DOHaD). This concept is grounded in much medical observation literally from ancient times but is more recently based on robust evidence that early development, particularly fetal development, profoundly influences lifelong health.[202] The model arose from numerous retrospective epidemiological studies showing associations between sub-optimal events or circumstances during fetal development, particularly maternal undernutrition often resulting in altered growth and low birth weight, and later life cardio-vascular disease, type 2 diabetes, or their biomedical risk factors including obesity and metabolic syndrome, as well as malignancies, osteoarthritis and dementia.[203,204,205,206] The rising incidence of low birth weight in Canada (as described in Section 2.0 above) over the last twenty years is notable in this context.

The DOHaD model has been further demonstrated across experimental animal studies, prospective clinical studies and additional epidemiological studies to strongly suggest that environmental factors during fetal development, as well as during early child development, can significantly influence lifelong disease risks.[207] In this paradigm, "environmental" factors are not equivalent to the environmental concepts previously discussed in Sections 3 and 5 above, such as exposure to toxic substances or broader environmental issues like the health effects of climate change. Rather, in the DOHaD model, the early "environment" refers to a broader array of factors that influence normal fetal development such as maternal age, health status, nutrition, stress levels, etc.

Complex biochemistry (discussed further in Section 8.3 below) underlies the growing scientific understanding of the response in the developing mammal, also referred to as "developmental programming", to specific challenges during critical windows or periods of vulnerability. The biochemical response to these challenges can alter the trajectory of development and permanently change disease susceptibility in the organism, including passing on this susceptibility to subsequent generations.[208]

This description will sound very familiar to those with an understanding of the concept of "windows of vulnerability" as it is used to describe concerns about the greater vulnerability of the developing fetus or young child to environmental contaminants. Herein is a key nexus between the work of CPCHE and OCDPA.

The DOHaD model reveals how specific aspects of fetal development, such as undernutrition leading to low birth weight, contribute to later development of chronic diseases. Since some environmental contaminants, are also known to contribute to low birth weight, such exposures need to be considered in the assessment of the lifetime impacts of low birth weight.[209] These and other examples of this nexus are discussed in the disease-focused sections below.

Although there are many uncertainties and knowledge gaps in the field of children's environmental health, the distinct vulnerability of fetal development is not among them. As described in Section 3.2 above, extensive evidence confirms that across the entire course

202 Gluckman PD and Hanson MA (2004) Living with the Past: Evolution, Development, and Patterns of Disease. *Science;* 305:1733-1736.
203 Barker DJP (1995) Education and debate: Fetal origins of coronary heart disease, *British Medical Journal*; 311:171-174.
204 Erikkson JG (2005) The fetal origins hypothesis – 10 years on. Editorial, *British Medical Journal;* 330:1096-1097.
205 Barker DJ and Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*;1(8489):1077-81.
206 Barker DJ et al (1993) Fetal nutrition and cardiovascular disease in adult life. *Lancet;* 341(8850):938-941.
207 Hanson MA and Gluckman PD (2008) Developmental Origins of Health and Disease – New Insights. MiniReview. *Basic and Clinical Pharmacology and Toxicology;* 102:90-93.
208 Niljand MJ et al (2008) Prenatal origins of adult disease. *Current Opinion in Obstetrics and Gynecology;* 20:132-138.
209 Porta M et al (2009) Transgenerational inheritance of environmental obesogens. *Occupational and Environmental Medicine;* 66(3):141-142.

of fetal development there are multiple times of extreme vulnerability to environmental contaminants.[210,211] These vulnerabilities vary with developmental stages. To note only two of many possible examples, during early pregnancy, if exposure occurs to teratogenic substances such as some solvents or pesticides, fetal vulnerability can manifest in structural deformities or birth defects. In later pregnancy, after major morphological development is complete, exposure to known developmental neurotoxins such as lead, mercury or PCBs, can result in more subtle impacts on later brain functioning.

The DOHaD model underpins this fetal vulnerability and response to environmental variation, in the broadest meaning of the word "environment." As this research has continued, the primary mechanisms at work are increasingly understood to be the interplay between genetics and epigenetics. Hence, in the reviews of chronic diseases below, the evidence about the epigenetic influences of environmental contaminants is frequently revisited.

8.2 Epigenetics

Beginning in the early 1990s, work progressed to understand and map the human genome, that is, the entirety of the genetic and hereditary information encoded in human DNA, completed in 2003.[212] Alongside this work, the field of epigenetics expanded dramatically. Epigenetics refers to inherited changes in appearance or gene expression that do not arise from corresponding changes in the underlying DNA sequence. It can literally mean "in addition to changes in genetic sequence,"[213] though there is ongoing debate about how to define what is a rapidly growing and highly complex field of study.[214]

In comparative terms, genetics and epigenetics can be viewed as two mechanisms for expressing the underlying genetic code in DNA, including any changes or mutations that may occur and influence the development of disease. For example, it has long been understood that cancer can develop as a result of genetic mutations. However, epigenetic changes are also involved that can change the timing or frequency of how a gene is expressed rather than changing the underlying genetic code or DNA sequence itself.[215]

Complex biochemistry is at work in the interaction and manifestation of the genome and epigenome. This interaction is particularly strong during the sensitive early stages of life,[216] although epigenetic processes continue throughout life. Across the myriad processes of cellular differentiation that occur during the development of any organism, the result is a combination of epigenetic and genetic inheritance. Clearly, this cellular differentiation process relies heavily on the epigenetic rather than the genetic inheritance.

Also referred to as "the science of change," the environmental influence on the expression of the epigenome occurs via many drivers. These changes can be both biochemical (e.g., via diet, toxic substances or radiation, viruses, bacteria, etc.) and behavioural.[217] For example, it has long been understood that the expression of the epigenome in brain development is affected by behaviour, for example of the mother, and experience. Moreover, this relationship is bi-lateral: behaviour can affect epigenetic programming and vice versa.[218] The DOHaD model and these underlying epigenetic mechanisms are apparent in the evidence discussed in Section 6 above concerning experienced-based brain development affecting multiple aspects of lifelong health.

210 Selevan SG et al (2000) Identifying critical windows of exposure for children's health. *Environmental Health Perspectives*; 108:451-455.
211 Landrigan PL et al (2004) Children's health and the environment: public health issues and challenges for risk assessment. *Environmental Health Perspectives*; 112:257-265.
212 Human Genome Project Information: http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml
213 Weinhold B (2006) Epigenetics: The Science of Change. *Environmental Health Perspectives;* 114(3): A160-67.
214 Bird A (2007) Perceptions of epigenetics. *Nature;* 447:396-98.
215 Dworkin AM et al (2009) Epigenetic alterations in the breast: implications for breast cancer detection, prognosis and treatment. *Seminars in Cancer Biology*; 19:165-171.
216 Tremblay J and Hamet P (2008) Impact of genetic and epigenetic factors from early to later disease. *Metabolism Clinical and Experimental* 57(*Suppl* 2):S27–S31.
217 Weinhold B (2006) Epigenetics: The Science of Change. *Environmental Health Perspectives;* 114(3):A160-7.
218 Szyf M et al (2008) The Social Environment and the Epigenome. *Environmental and Molecular Mutagenesis;* 49:46-60.

Across many different illnesses, behaviours and other indicators of health, evidence is emerging of underlying epigenetic mechanisms. In animal studies over the past 20 years and in a small number of recent human studies, epigenetic mechanisms have been increasingly linked to cancer, obesity and diabetes, infertility, respiratory disease and asthma, allergies and immune responses, neurodegenerative disorders, stress responses, and more.[219] The strength of evidence varies for different illnesses and conditions and the role of environmental contaminants is one part of this emerging science.

As evidence grows it is demonstrating epigenetic processes underlying the toxicity of many environmental exposures of concern including heavy metals, pesticides, diesel exhaust, tobacco smoke, PAHs, and radioactivity. For example, in some cases, epigenetics is helping to explain underlying mechanisms of otherwise very well established associations, such as the neurotoxicity[220] and carcinogenicity[221] of lead as a result of *in utero* exposure. More broadly, some evidence[222] indicates that epigenetic changes at the cellular level caused by chronic stress (such as inflammation or oxidative stress) may lock in the early stages of common chronic diseases (cancer, cardiovascular disease, diabetes, etc.). As these heritable changes (during subsequent cellular renewal) then drive the appearance and progression of disease, underlying epigenetic mechanisms help to explain these long-known associations between cellular stress and these common chronic diseases. Concern is particularly heightened about the interaction of endocrine disrupting compounds with epigenetic processes given the role of the endocrine system in orchestrating the many complex stages of human development. Epigenetics is therefore highly relevant to understanding the evidence about early exposures to chemical substances and the development of chronic disease.

In summary, considerable evidence, briefly outlined above, and further explored in the chronic disease-focused sections below, points to the *in utero* and perinatal environment as playing a major role in the risk of later life disease.

8.3 Evaluating Evidence

Throughout Part One, where this report discusses the evidence base for the many contextual issues raised, the type of available evidence is noted. This approach continues in the review of evidence in Part Two.

It is obviously important when statements are made or conclusions are drawn to be aware of the strength of evidence supporting them. Thus far, summary information is presented in four major areas noting strong evidence for:

- the large and growing importance of multiple chronic diseases in the Canadian population;
- the primary importance of the social determinants of health in contributing to health and chronic disease;
- the developmental origins of health and disease; and
- the greater vulnerability of the fetus and child to environmental contaminants.

Before turning to the reviews of evidence (in Sections 8-13 below) concerning associations between environmental exposures and chronic diseases, it is important to discuss key issues that arise with such scientific investigations. These issues fundamentally challenge our ability to understand and take action on the early environmental exposures that are known to, or can potentially play a role in chronic disease.

219 Edwards TM and Myers P (2007) Environmental Exposures and Gene Regulation in Disease Etiology. Review. *Environmental Health Perspectives*;.115(9):1264-1270.

220 Pilsner JR et al (2009) Influence of Prenatal Lead Exposure on Genomic Methylation of Cord Blood DNA. *Environmental Health Perspectives;* 117(9):1466-1471.

221 Silbergeld E et al (2000) Lead as a carcinogen: experimental evidence and mechanisms of action. *American Journal of Industrial Medicine;* 38(3):316-323.

222 Johnstone SE and Baylin SB (2010) Stress and the epigenetic landscape: a link to the pathobiology of human diseases? *Nature Reviews Genetics*; 11:806-812.

The great complexity involved has been noted. Central to this complexity is the fact that all chronic health outcomes are the result of multiple, inter-related factors that can also be spread across many years or decades prior to disease onset. Further, some chronic diseases or their risk factors, such as hypertension, obesity and diabetes, are also risk factors for other chronic diseases such as cardiovascular disease, cancer and Alzheimer's disease. Challenges relate to study design, evidence hierarchies, and numerous barriers to establishing causality inherent in the environmental sciences.

8.3.1 *Study Design and Evidence Hierarchies*

To assist understanding of key issues in determining health links with environmental exposures, a brief discussion is needed of the types of research studies and by their design, the strength or weight that is attached to them. For the purposes of clarity, this discussion does not address the methodologies that distinguish between good and poor quality studies, such as the efforts to reduce bias and confounding and thus enhance internal validity, or to evaluate applicability/generalizability to other circumstances (external validity). There are many tools available to assist in systematically and critically appraising methodological quality, although there is considerable variation among them.[223,224]

Rather, it is the framework – the hierarchy of evidence – developed by the community working on evidence-informed decision making that poses challenges for environmental health issues. There are a variety of proposed evidence hierarchies often depicted in pyramids. The hierarchy or an evidence pyramid presupposes greater weight, based on better design and less uncertainty, for those study types that are higher up on the pyramid (See Figure 3). The premise behind such a pyramid is reasonable in the sense that individual cell culture or animal studies, while adding to the body of literature, are not to be weighted the same as a quality randomized controlled trial in a human study population that measures an intervention as accurately as possible and is careful to control for confounders. Similarly, a meta-analysis or systematic review that attempts to bring together findings of many studies examining a similar endpoint is weighted more heavily than one lone study, presuming that these syntheses are done using strong methodology.

Figure 3: The Evidence Pyramid[225]

223 Katrak P et al (2004) Systematic review of the content of critical appraisal tools. *BMC Medical Research Methodology*; 4:22 doi:10.1186/1471-2288-4-22.

224 Vlayen J et al (2005) A systematic review of appraisal tools for clinical practice guidelines: multiple similarities and one common deficit. *International Journal for Quality in Health Care*; 17(3):235-242.

225 Source: State University of New York Downstream Medical Centre (2004) Evidence Based Medicine Tutorial, Guide to Research Methods. http://library.downstate.edu/EBM2/2100.htm

This sort of hierarchy works well for drug trials where the treatment (or exposure) is specific, applied to individuals with defined inclusion and exclusion criteria, and measured outcomes are compared with similarly selected individuals receiving a placebo or other drug. Outcomes (as objective as possible) are measured in the study subjects and potential confounders and bias are minimized. However, this approach cannot apply to the area of environmental health because it is unethical to knowingly expose individuals or a population to an environmental contaminant for the purposes of studying its impacts where no health benefits are anticipated. For this reason, studies linking environmental exposures to an adverse health outcome in humans are observational studies where an exact exposure (amount, timing, route) cannot be confirmed for the study subjects, and there may not be good measurements of health outcomes available. Observational designs include cohort and case-control studies, case reports, and ecological studies where population-level exposure indicators are used (e.g. ambient air monitoring).

Based on most hierarchies of evidence, observational studies of potential associations between environmental exposures and health outcomes are considered lower level, or relatively weak, as they cannot reach the methodological rigour of those higher levels on the pyramid. In the case of a few environmental health issues biological markers of exposure (e.g. blood lead, saliva cotinine) have been useful in linking personal exposure to environmental levels.

Authors of the GRADE system to classify strength of evidence, note that while observational studies may start as low level evidence, moving up the hierarchy may be warranted particularly if there is evidence of a dose-response relationship.[226] Similarly, there may be other Bradford Hill criteria for assessing causality such as analogy (as discussed further below) that may be satisfied even with lower level evidence.

Very few causal relationships between environmental exposures and human health impacts have been firmly established. However, like cigarette smoking, the strength of associations are often well established for many years prior to finding causal evidence, the latter generally considered to have been verified once scientists can add to the evidence of associations (from both animal and human epidemiological data) a clear determination of the mechanism of action whereby disease occurs.

For the health outcomes discussed in the balance of this report, the scientific evidence about suspected associations with certain exposures is described. Prevalence data are also provided. Only rarely is there sufficient scientific evidence to trace a direct or causal relationship between the prevalence of these health outcomes in the population and specific environmental exposures.

For example, it is now well established, up to and including causal evidence, that multiple human health effects arise from substances such as asbestos, lead, methylmercury, organic solvents, the CACs, and several POPs (including the OC pesticides, PCBs, dioxins and furans). Less conclusive evidence exists for the toxicity of additional substances but, in general, vast uncertainty remains for thousands more substances that are suspected of causing harm but are poorly investigated.

There are public health implications of waiting for scientific certainty, including the desire for epidemiological evidence to complement animal/laboratory evidence, before taking preventive or precautionary action.

8.3.2 Indirect Evidence and Multi-causality

It would never be ethical to run controlled experiments on human subjects to determine the safety of exposure to environmental contaminants.

Instead of directly controlled experiments such as are more typical for testing pharmaceuticals, various lines of indirect evidence are gathered, the overall weight of evidence is assessed and often described as sufficient, limited or inadequate to conclude whether an environmental agent is actually associated with a specific effect.[227] Evidence can include studies on humans, sometimes from occupational exposures or accidents or epidemiological evidence of health effects

226 Guyatt GH et al (2008) Rating Quality of Evidence and Strength of Associations. GRADE: going from evidence to recommendations. *British Medical Journal*; 336(7652):1049-1051.

227 Wigle D (2003) *Child Health and the Environment*. Oxford University Press.

in a specific population. Animal evidence comes from studies of wildlife or controlled laboratory experiments studying specific effects at specific exposure levels, either *in vivo* ("in the animal") or *in vitro*, (literally, "in glass") using tissue or cell cultures; the latter can also be done on human tissue or cell cultures.

Hence, not only must scientists rely on incomplete and indirect evidence, it is extremely rare that such investigations include, or are even capable of considering, the combined effect of multiple chemical exposures. While advances are being made in the laboratory testing of chemical mixtures in terms of methods to assess the combined effects of several substances, significant challenges remain. Complex techniques are being developed to assess groups of similar pesticides[228] and more recent proposals have been made to assess the health endpoints associated with groups of phthalates.[229] However, epidemiological studies are inherently limited in this regard. Humans are continuously exposed to mixtures of chemicals, some of them acting through common metabolic pathways making it extremely difficult to isolate relationships between specific exposures and effects.

Similarly, investigations into the toxicity of chemical exposures rarely address the issue of multi-causality. As noted in Sections 5 and 7 above with respect to the many interrelationships that are apparent within the MDOH framework, and particularly with respect to environmental exposures, the history of the public health sciences continues to exhibit a "creative tension" between a mono-causal, reductionist approach to disease investigation and more holistic, multi-causal approaches.[230] A clear example is paper by Canadian public health experts[231] offering a framework for applying the precautionary principle to public health issues. These authors uncritically advance the Bradford Hill criteria for assessing causation absent any recognition of a rich debate in the literature concerning barriers and challenges to their applicability given the multi-causal nature of environmental health issues (as discussed further below).

8.3.3 The Bradford Hill "Criteria" for Assessing Causation

In 1965, while recognizing the multi-causality of disease but working essentially within a mono-causal paradigm, Sir Austin Bradford Hill wrote about causation and environmental health and laid out nine characteristics of scientific evidence that, if viewed together, can assist in considering whether an association is causal.[232] Although he stated emphatically that these characteristics should not be considered "hard-and-fast rules of evidence that must be obeyed before we can accept cause and effect," they are still referred to as the "Bradford Hill criteria," are widely used, and often expected to be broadly met. Notably, the European Environment Agency has stated the need for their review and has stated that it intends to do so as part of its 2009-2013 Strategy.[233]

It is important to review the so-called "Bradford Hill criteria," and the ongoing critique of them, (explored below), in the context of a discussion about evidence for environmental impacts on health. The Bradford Hill criteria include the following:

Strength of the association

(a clear difference is observable between an exposed and unexposed population; Bradford Hill cautioned that a relationship not be dismissed if an observed association is slight)

Consistency of the association

(multiple studies finding the same results and under different circumstances)

228 U.S. Environmental Protection Agency (2011) Assessing Pesticide Cumulative Risk. See multiple publications at: http://www.epa.gov/oppsrrd1/cumulative/

229 National Research Council of the National Academies (2008) *Phthalates and Cumulative Risk Assessment – The Tasks Ahead*. National Academies Press, Washington DC.

230 Gee D (2008) Establishing Evidence for Early Action: the Prevention of Reproductive and Developmental Harm. MiniReview in *Basic and Clinical Pharmacology and Toxicology;* 102: 257-266.

231 Weir E et al (2010) A Canadian Framework for Applying the Precautionary Principle to Public Health Issues. *Canadian Journal of Public Health*; 101(5):396-398.

232 Bradford Hill A (1965) The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*; 58:295-300.

233 European Environment Agency (2009) *EEA Strategy 2009-2013, Multi-annual Work Programme*.

Specificity of the association

(the association is limited to specific exposures and specific types or sites of disease; not to be overemphasized given that diseases are multi-causal)

Temporality of the association

(the observed disease occurred after the exposure and not before)

Biological gradient observable for the association

(the evidence indicates a dose-response curve, where one can be determined)

Plausibility of the association

(the finding of an association is consistent with known biology although Bradford Hill cautioned that this characteristic depends on existing knowledge which can be incomplete and the study may disclose new information)

Coherence of the facts involved

(despite the potential for the study being conducted in the context of incomplete knowledge, the finding is not in serious conflict with existing knowledge)

Experiment (recovery or reversibility)

(a confusing term since it was not meant by Bradford Hill to mean the association can be demonstrated by experiment but whether it can be reversed via removal of the suspected causal factor)

Analogy of the study results

(the results can be considered comparable to other similar situations where there may be more evidence)

These study characteristics remain useful signposts for judging the overall strength of an association. By extension, evidence strength derives from individual study characteristics such as the greater reliability of results from a prospective or longitudinal cohort study as compared to a cross-sectional or case-control study. For example, in a prospective study, temporality can be demonstrated and investigators can conduct ongoing exposure measurement without having to rely on potentially erroneous or biased recall by study participants as can occur in a more limited cross-sectional study. Likewise, statistical techniques, such as meta-analysis, can assist with the determination of associations by combining results of multiple studies.

Nevertheless, experts note[234] that for complex environmental health issues the Bradford Hill criteria are overly simplistic tools that rest upon inherent assumptions about mono-causality and are inadequate to the task of describing or evaluating the multi-causal, complex and dynamic processes that contribute to disease. Indeed, they note that tools to unravel this complexity are in their infancy. For example, many examples of bidirectional or reciprocal relationships, literally circular causation, have been identified in the study of tissue organization during human development as well as in studies of carcinogenesis.[235] These results challenge the validity of strict adherence to temporality, considered one of the most important of the Bradford Hill criteria. Another example is the model of inter-relationships between social environments, micronutrients and neurotoxicants noted in Section 7 above (and illustrated in Figure 2). In this example, even for well-studied toxic substances such as lead, complex and bidirectional relationships are seen between interacting factors such as lead exposure, neurotoxicity and social enrichment or deprivation.[236]

The traditional approach in epidemiological studies of rigorously eliminating confounders from an analysis, for example removing social environment factors from research into lead toxicity, has been shown to actually eliminate co-causal factors and thus weaken and/or misrepresent true

234 Gee D (2008) Establishing Evidence for Early Action: the Prevention of Reproductive and Developmental Harm. *Basic and Clinic Pharmacology and Toxicology;* 102:257-266.

235 Soto A and C Sonnenschein (2006) Emergentism by default: A view from the bench. *Synthese;* 151:361-376.

236 Rauh VA et al (2003) Biological, social, and community influences on third-grade reading levels of minority Head start children: a multilevel approach. *Journal of Community Psychology;* 31(3):255-278.

associations.[237] The inherent complexity of these interrelationships and the diversity of human epigenetics are also considered to create sufficient variability that the criterion of consistency may not be met as often as might be expected if the Bradford Hill criteria are applied from a limited, mono-causal standpoint.

The reality of many-to-many relationships and the fact that some highly toxic substances such as lead, mercury, asbestos, and POPs are known to be associated with multiple health endpoints, undermines the notion of insisting upon the criterion of specificity. While important, it should not be given undue weight given that substances capable of causing multiple harmful effects are qualitatively and quantitatively different, and generally much more dangerous, than those for which associations are seen for only one health end-point. The complexity of the systems under consideration, particularly during dynamic periods of development, as well as the persistence of some toxic substances in the environment points to the need to also avoid giving too much weight to the criterion of experiment (or reversibility) given how long it can take for ecosystems to recover from contamination.

Many substances that are of concern during sensitive stages of human development, including but not limited to endocrine-disrupting substances, challenge another of the key Bradford Hill criteria, that of a biological gradient. While a linear dose-response relationship is a logical and important criterion in many instances, during vulnerable life stages the timing of exposure is more important where a dose that will not affect an adult can do serious harm to a fetus. For substances that can interfere with the endocrine system, a linear relationship can be irrelevant and misleading. Rather, where a dose-response curve is non-monotonic or U-shaped, seen with endocrine-disrupting substances like BPA, effects that can occur at extremely low doses during development do not occur at much higher levels.

Conversely, two of the Bradford Hill criteria that experts consider should, carefully, be given greater weight in environmental health matters are analogy and plausibility. Bradford Hill illustrated the issue of analogy with examples directly relevant to fetal vulnerability, i.e., the drug thalidomide and the rubella virus, noting that such situations should lend support to exercising caution in analogous situations where evidence may be less robust. Combining analogy with biological plausibility is also valuable to address the vast number of environmental contaminants where strong evidence that exists for a small number of substances can be considered relevant to those that are less studied. Caution is necessary here given that much evidence exists for large differences in toxicity of similar chemicals despite very minor differences in chemical structure.

Bradford Hill noted strength of the association as the first characteristic of studies, implying it was of top importance. However, he also stated that only slight associations should not be dismissed and he strongly cautioned against excessive reliance on statistical tests of significance noting that such reliance can result in incorrectly concluding “no difference” from “no significance.”[238]

Another perspective[239] on the Bradford Hill criteria makes a distinction between two different views of causality: the probabilistic regularity view and the generative view. In the first, they contend that causality is based on observed assocations between the effect and a potential causal factor, and this approach allows for the influence of other factors in a common causal complex. For this probabilitic view, the criteria of strength, specificity, consistency, experiment and biological gradient are most effective in explaining causal associations. In the generative view, the focus is placed on explanations provided by networks of mutually related associations and therein the use of the criteria of coherence, plausibility and analogy. Temporality fits uniquely within neither view but obviously assists in both cases by inferring direction from cause to effect. The authors of this study note that these two views are useful under different circumstances. They further note that these differences across the Bradford Hill criteria illustrate limitations that should be included when discussing or applying them.

237 Bellinger D (2007) Lead neurotoxicity in children: Decomposing the Variability in Dose-Effect Relationships. *American Journal of Industrial Medicine;* 50:720–728.

238 Bradford Hill A (1965) The Environment and Disease: Association or Causation*? Proceedings of the Royal Society of Medicine*; 58:295-300.

239 Thygesen LC et al (2005) A philosophical analysis of the Hill criteria. *Journal of Epidemiology and Community Health*; 59:512-516.

8.3.4 *The Preponderance of Type II Errors in Environmental Case Studies*

In statistical calculations of significance, Type I errors involve accepting spurious associations (also referred to as "false positives") as causal when in fact they are not. Type II errors ("false negatives") are those that miss true causal associations. It is a confusing concept because of the double negative. In simpler terms, Type I errors occur when we conclude one event causes another when in fact it does not. Type II errors occur when we conclude that two events are unrelated when in fact one causes the other. The importance of avoiding Type I errors is universally recognized in the conduct of scientific investigations for many reasons but it can result in true associations being missed.

Many examples exist of Type II errors (i.e., missing causal associations) occurring in matters of environmental contamination, including impacts on human health. For example, in studies of the effect of lead on IQ, (now clearly understood from many years of research to be a causal relationship), six flaws in study design or interpretation have been identified that systematically reduced the risk of Type I errors at the cost of increased risk of Type II errors.[240] In a review of study designs for a broader range of environmental health issues across experimental animal studies, observational studies in wildlife and humans, and considering the scientific pressure to avoid Type I errors, a systematic bias was also found towards Type II errors, with the result that the avoidance of "false positive" results was at the expense of generating "false negative" results.[241] Multiple examples of this problem are also identified by the European Environment Agency in a detailed report about the need for greater precaution in environmental decision-making including the need for prudent action to reduce or eliminate exposures in the face of limited but troubling evidence of associations.[242]

8.3.5 *Challenges to How Risk Factors are Defined*

In the following discussions in Sections 9 – 13 about the evidence linking early environmental exposures and chronic diseases, early exposures are discussed in the context of current knowledge about multiple contributing risk factors. The evidence is also described in terms of strength and type, particularly where animal evidence is complemented by epidemiological data.

More detail is noted about early life environmental risk factors in the context of other known risk factors. Further to the discussion in Part One about the value of the MDOH model, it should be recalled that social and environmental risk factors create important challenges to the traditional public health approach to defining risk factors. On the environmental side, this challenge arises in part from the demand for epidemiological evidence to confirm and complement the broader evidence base. For example, the federal government's *Chronic Disease Risk Factor Atlas*[243] notes the following widely-accepted definition for a risk factor:

> an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that, **on the basis of epidemiologic evidence**, is known to be associated with health-related condition(s) considered important to prevent (emphasis added).[244]

This definition does not adequately recognize the social aspects of "lifestyle" that are often beyond personal control, as discussed in Section 2.3.2 above. As well, in the context of environmental exposures, particularly those that may fundamentally alter the life course via impacts on prenatal or perinatal development, this demand for epidemiological evidence to confirm the existence of a chronic disease risk factor has major implications.

Quite simply, awaiting epidemiological evidence for impacts of early environmental exposure is too late to prevent serious and often irreversible harm. An often-repeated lesson of environmental policy is the importance of taking action when stakes are high, even in the face of incomplete

240 Bellinger D and H Needleman (1991) The health effects of low level lead exposure. *Annual Review of Public Health;* 12:111-40.
241 Grandjean P (2005) Non-precautionary aspects of toxicology. *Toxicology and Applied Pharmacology*; 207:652-7.
242 European Environment Agency (2001) *Late lessons from early warnings: The precautionary principle 1896-2000*.
243 Government of Canada (2008) *Chronic Disease Risk Factor Atlas*.
244 From: Last JM (ed.) (2001) *A Dictionary of Epidemiology* 4th ed. New York: Oxford University Press; p. 160.

evidence. By the time epidemiological evidence may be available, widespread exposure will have occurred that can be difficult or even impossible to remove and large vested interests are often at stake in society, a fact that often makes resolution of the problem far more difficult.

Defining a risk factor as arising from epidemiological evidence is inherently limiting in the context of environmental exposure situations where there is typically animal evidence alone, or very limited epidemiological evidence. Rather, animal evidence, viewed in light of the Bradford Hill criteria of analogy and plausibility, can serve as a warning of a potential problem in humans and prompt precautionary action prior to allowing widespread and/or continued exposure.

The history of lead pollution from its use in gasoline is a classic example of awaiting extensive epidemiological evidence of harm before taking regulatory action and long after widespread and largely irreversible contamination had occurred.[245] Despite the good news that lead levels in the human population have continued to drop after the phase-out of lead in gasoline and other sources,[246] as noted in Section 3.1.1 with respect to biomonitoring results, current blood-lead levels remain over 100 times higher than the pre-industrial norm,[247] evidence indicates no lower threshold for toxic effects in children,[248] and prenatal lead exposure is implicated in several of the chronic diseases discussed below.

Similarly, for a substance like BPA, where epidemiological evidence is very limited, many of the health effects, or biochemical precursors to these health effects, observed in laboratory animal research, parallel the most common and/or increasing chronic health conditions in the human population including obesity, breast and prostate cancers, as discussed further in Sections 10 and 12 below. These and other environmental exposure examples underscore the arguments for elevating the Bradford Hill criteria of analogy and plausibility in order to more prudently recognize early environmental exposures as chronic disease risk factors as well as recognizing that epidemiological evidence does not tend to become available until long after widespread exposure and often irreversible environmental contamination has occurred.

8.4 DOHAD, Epigenetics and Evaluating Evidence – Key Points

- This section introduces additional context informing this discussion of early life environmental contaminant exposures and later life chronic disease.
- The Developmental Origins of Health and Disease (DOHaD) explores the associations between adverse events during vulnerable, early life stages and later life patterns of health and disease, such as the relationship between maternal prenatal undernutrition, low birth weight and increased risks for metabolic syndrome, diabetes, cardiovascular disease, malignancies, osteoarthritis and dementia in adulthood.
- Considerable evidence points to the *in utero* and perinatal environment as playing a major role in the risk of later life disease. "Environment" here is broadly defined to include maternal age, health status, nutrition, stress levels, etc. However, the similar concept of "windows of vulnerability" describes the greater vulnerability of the developing fetus or young child to environmental exposures during early life. Herein is a key nexus between the work of CPCHE and OCDPA.
- Epigenetic processes, gene-environment interactions which lead to changes in the expression of genes without change in DNA sequences, are seen as one important explanatory mechanism for DOHaD.
- Epigenetics processes likely underlie the toxicity of many environmental exposures of concern and therefore, are highly relevant to understanding the evidence about early exposures to chemical substances and the development of chronic disease.
- The Bradford Hill criteria for causation provide useful signposts for judging the overall

245 Cooper K and Vanderlinden L (2009) Pollution, Chemicals and Children's Health. In: *Environmental Challenges and Opportunities*, Chapter 8. Gore CD and Stoett, PJ (eds) Emond Montgomery (Toronto).

246 Bushnik T et al (2010) Lead and bisphenol A concentrations in the Canadian population. *Health Reports;* 21(3):7-18. Statistics Canada Catalogue no. 82-003-XPE

247 Flagel AR and Smith DR (1992) Lead levels in preindustrial humans. *New England Journal of Medicine;* 326(19):1293-1294.

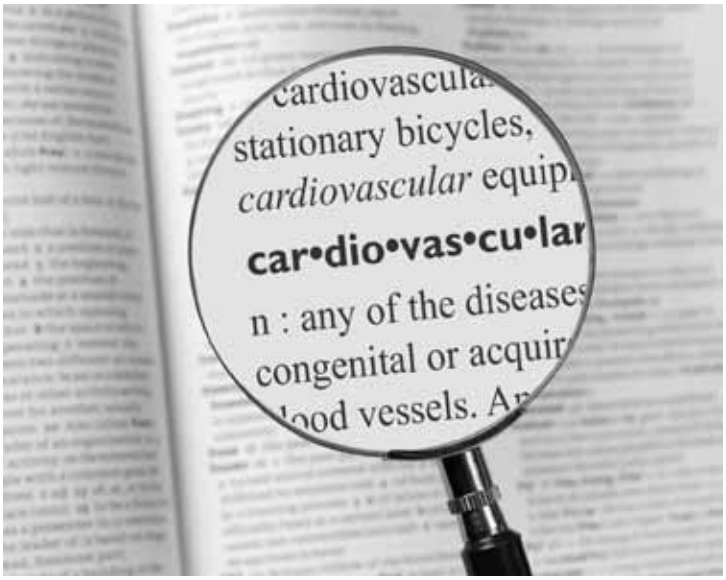
248 Bellinger DC (2008) Very low lead exposures and children's neurodevelopment. *Current Opinion in Pediatrics*; 20:172-177.

strength of an association and by extension, strength of a body of evidence, however, they can be inadequate to the task of evaluating the complex and dynamic processes that contribute to disease in a multi-causal model.

- Indeed, for environmental exposures that may fundamentally alter the life course via impacts on prenatal or perinatal development, a demand for epidemiological evidence to confirm the existence of a chronic disease risk factor has significant implications. Application of the Bradford Hill criteria of analogy and plausibility could be more prudently applied to early environmental exposures in the context of recognizing that epidemiological evidence does not tend to become available until long after widespread exposure and often irreversible environmental contamination has occurred.

9.0 Cardiovascular Disease

Cardiovascular disease (CVD) and injury can occur throughout the cardiovascular system including the heart, veins and arteries. CVD also includes stroke, a brain injury, resulting from problems with blood flow to or within the brain.



9.1 Prevalence of Cardiovascular Disease in Canada

CVDs among Canadians have declined dramatically and steadily since the 1950s.[249] As summarized in Table 2 in Section 2.1 above, heart disease and stroke, alongside cancer, remain the top three leading causes of death in Canada by a considerable margin (60% of all deaths in 2006). Statistics for 2005-2006 reveal that mortality rates[250] show a slight decline for both CVD and cancer as well as an indication that cancer is overtaking CVDs as the leading cause of all deaths in Canada although CVD remains the leading cause of death for women.[251]

In 2006 CVD continued to be the leading cause of hospitalization in Canada with 1.6 million Canadians reported to be living with heart disease or the effects of stroke. Over half (54%) of these deaths were due to ischemic heart disease (plaque on the walls or arteries in the heart interfering with blood supply to the heart muscle), 20% to stroke, and 23% to heart attack (interrupted blood supply to the heart).[252] In 2007, heart disease and stroke together accounted for 30% of all deaths (just over 69,000 people) in Canada while cancer and CVD accounted for 59% of all deaths in 2007.[253] More recent cancer statistics are noted in Section 12.1 below.

Strokes affect over 50,000 Canadians per year; about 300,000 Canadians are living with the effects of stroke and, for 2006, strokes killed 14,000, comprising 6% of all deaths.[254] Further, every year, about 15,000 people in Canada experience a Transient Ischemic Attack, or so-called mini-stroke, while many more go unreported.[255]

Additional CVDs or conditions include hypertension (high blood pressure – also a risk factor for CVD), cardiac arrythmias, heart failure and congenital heart disease (heart defects existing at birth). The latter are the most common of all birth defects affecting about one percent of all births in Canada or about 3500 births per year, though the most recently available trend data are from the 1990s.[256] Considerable range is apparent in these heart defects with some being a tiny hole in the heart never requiring treatment up to life-threatening conditions. About 100,000 adults living in Canada had surgery as children to correct congenital heart defects.[257]

249 Heart and Stroke Foundation of Ontario. Current information available at http://www.heartandstroke.on.ca/site/c.pvI3IeNWJwE/b.3581729/k.359A/Statistics.htm#decline
250 These mortality rates are age-standardized to account for an aging population.
251 Statistics Canada (2009) Leading causes of death in Canada, 2005. Available at http://www.statcan.gc.ca/pub/84-215-x/84-215-x2009000-eng.htm
252 Public Health Agency of Canada (2009) *Tracking Heart Disease and Stroke in Canada*.
253 Statistics Canada (2010) Mortality, Summary List of Causes 2007. Catalogue No. 84F0209X
254 Statistics Canada, CANSIM Table 102-0529: Deaths, by cause, Chapter IX: Diseases of the circulatory system (I00 to I99), age group and sex, canada, annual (number), 2000 to 2006. Released May 4, 2010.
255 Field TS et al (2004) Trends in stroke occurrence in Calgary *Canadian Journal of Neurological Sciences*; 31:387-393.
256 Health Canada and Canadian Perinatal Surveillance System (2002) *Congenital Anomalies in Canada - A Perinatal Health Report, 2002*.
257 Silversides CK et al (2010) Canadian Cardiovascular Society 2009 Consensus Conference on management of adults with congenital heart disease. *Canadian Journal of Cardiology*; 26(3):143-150.

9.2 Cardiovascular Disease Risk Factors

CVDs are complex chronic conditions with multiple risk factors, many of which are also risk factors for other conditions discussed in subsequent sections of this report.

To introduce this discussion of CVD risk factors, metabolic syndrome should be highlighted since it describes a group of disorders that individually or in combination are often antecedent conditions to CVD and other chronic diseases including cancer, diabetes and Alzheimer's disease. Metabolic syndrome can include increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure, and elevated fasting-glucose levels. Individuals with three of five of these criteria (all of which are among the risk factors for CVD, as discussed below) are considered to have metabolic syndrome.[258]

CVD risk factors are typically described as either "non-modifiable," such as genetics, gender and age, or "modifiable" including factors such as nutrition, a wide range of unhealthy behaviours, other health conditions, as well as environmental exposures. Much complexity exists within these two broad groupings, as discussed below.

Despite impressive statistics showing that heart disease and stroke in Canada has declined steadily and dramatically, by 75% between 1956 and 2006, the Heart and Stroke Foundation of Canada warns that:

> ***…a "perfect storm" of risk factors and demographic changes are converging to create an unprecedented burden on Canada's fragmented system of cardiovascular care, and no Canadian young or old will be left unaffected.***[259]

9.2.1 Non-Modifiable Risk Factors

It has long been known that some individuals have a genetic susceptibility to CVD which, when combined with behavioural risk factors, increases risk of CVD. Like genetic susceptibility to asthma, (discussed in Section 13.2 below), genetic susceptibility to CVD involves multiple genes that can influence many aspects of cardiovascular health, including blood lipids, blood pressure, obesity, insulin resistance and diabetes.[260] Part of the crisis of CVD occurring among Canada's Aboriginal population may stem from a genetic susceptibility to CVD or its risk factors. Genetic susceptibility also appears to be present among those of South Asian and African-Caribbean descent, the former being a particularly fast-growing segment of Canada's population.[261] Moreover, increased knowledge of the interaction between genetic and environmental risk factors, as discussed above in the context of epigenetic mechanisms in the early origins of disease, indicates that genetic susceptibility is not strictly a "non-modifiable" risk factor.[262]

In terms of gender and age, it remains the case that men are more susceptible to CVD but this gender gap is closing as multiple risk factors, particularly overweight and obesity, are setting up young women as a new "at-risk" population for later life CVD.[263] As well, CVD is no longer typified as largely a disease of older, Caucasian men. Large numbers of young adults in Canada are considered to be at risk for CVD given their increasing rates of all the major CVD risk factors including smoking, poor eating habits, physical inactivity, overweight and obesity, diabetes and hypertension.[264] In addition to evidence about rising rates of behavioural risk factors in young adults, researchers also note that precursor conditions to CVD can be present for many years.

258 Alberti KG et al (2009) Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*; 120:1640-1645.

259 Heart and Stroke Foundation (2010) *A Perfect Storm of Heart Disease Looming on Our Horizon*. 2010 Annual Report on Canadian's Heart Health.

260 Public Health Agency of Canada (2009) *Tracking Heart Disease and Stroke in Canada*. Chapter 3: The Genetic Epidemiology of Cardiovascular Disease.

261 Heart and Stroke Foundation (2010) *A Perfect Storm, op.cit*.

262 Genuis SJ (2008) Our genes are not our destiny: incorporating molecular medicine into clinical practice. *Journal of Evaluation in Clinical Practice*; 14(1):94-102.

263 Public Health Agency of Canada (2009) *Tracking Heart Disease and Stroke in Canada*. Chapter 2: Preventing Cardiovascular Disease.

264 Heart and Stroke Foundation (2010) *A Perfect Storm, op.cit*.

For example, in overweight or obese children the accumulation of fatty deposits can start early in life and get progressively worse. Such "fatty streaks" have been detected in children and may predispose them to CVD later in life.[265]

9.2.2 Modifiable Risk Factors

The so-called modifiable risk factors include those having to do with multiple behaviours, such as smoking or eating habits, and related biochemical conditions, such as high blood pressure, that are also potentially modifiable via behaviour change.

Two very large, international case-control studies of heart disease, the INTERHEART[266] and INTERSTROKE[267] studies (which include research teams from Canadian universities), have identified the major risk factors for heart attack and stroke respectively. There is nearly complete overlap between risk factors described in these two studies. The INTERHEART study concludes that, collectively, nine significant risk factors accounted for 90% of the population attributable risks (PAR) of myocardial infarction (heart attack) in men and 94% in women. These associations were noted for men and women, old and young, and in all regions of the world.

The INTERHEART risk factors for myocardial infarction (heart attack) include:

- abnormal lipids (that is, ratio of ApoB to ApoA1, or the measure of blood lipids commonly referred to as "high cholesterol")[268]
- smoking
- hypertension/high blood pressure
- diabetes mellitus (type 2 diabetes)
- abdominal obesity
- psychosocial factors (e.g., stress)
- daily consumption of fruits and vegetables (where this is limited or lacking)
- regular alcohol consumption
- regular physical activity (where this is limited or lacking)

The INTERSTROKE study makes similar conclusions about these same nine significant risk factors and adds as a tenth, cardiac causes (itemized below) to which are attributed 90% of the risk of stroke, both ischaemic stroke (interupted blood flow to the brain due to a blood clot – about 80% of strokes) and intracerebral haemorrhagic strokes (uncontrolled bleeding in the brain – about 20% of strokes). The INTERSTROKE study risk factors are described as follows:

- history of hypertension
- current smoking
- waist to hip ratio (comparable to abdominal obesity per INTERHEART study)
- diet risk score (greatest risk where there is limited consumption of fruits, vegetables and whole grains and excess consumption of fats, sodium and simple carbohydrates)
- regular physical activity (where this is limited)
- diabetes mellitus (type 2 diabetes)

265 McGill HC et al (2000) Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Arteriosclerosis, Thrombosis and Vascular Biology*; 20(8):1998-2004.

266 Yusuf F et al (2004) Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The Lancet*; 364:937-952.

267 O'Donnell MJ et al (2010) Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *The Lancet*; 376:112-123.

268 More specifically, this elevated ratio includes higher levels of ApoB, containing "bad" low density (LDL), intermediate density (IDL) and very low density (VLDL) lipid-transporting lipoproteins, and lower levels of ApoA1, containing high density lipoprotein (HDL) or "good cholesterol"). See: Walldius G and Jungner I (2006) The apoB/apoA-1 ratio: a strong new risk factor for cardiovascular disease and a target for lipid-lowering therapy - a review of the evidence. *Journal of Internal Medicine*; 259(5):493-519.

- alcohol intake (for more than 30 drinks per month or binge drinking)
- psychosocial stress and/or depression
- cardiac causes (including atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve)
- ratio of apolipoproteins B to A1 (i.e., abnormal lipids or "high cholesterol")

The INTERHEART investigators also separately evaluated psychosocial stressors and found they are independently associated with increased risk of acute myocardial infarction.[269] They note that several previous studies of smaller populations have found a relationship between work stress and heart attack. However, these studies, with data from the very large multi-country INTERHEART sample, are unique in simultaneously evaluating multiple elements of stress including perception of stress and life events (i.e., well beyond work-related stress) and using a questionnaire measure of locus of control (that is, the perceived ability to control life circumstances). The INTERHEART researchers conclude that for severe global stress, the size of the effect was less than for smoking but comparable with hypertension and abdominal obesity. They further conclude that if this relationship is truly causal, psychosocial factors are much more important than commonly recognized, and may be responsible for a substantial proportion of acute myocardial infarction.

These conclusions lend support to analyses arising in the literature about the SDOH. In line with the idea of addressing the "causes of the causes" (discussed in Section 4.3) the biomedical and behavioural risk factors for cardiovascular disease are seen as arising from social and economic conditions, particularly the circumstances of poverty. Notably, the INTERHEART findings indicated greater stress and corresponding greater risk of CVD when life circumstances were perceived to be beyond personal control.

As noted in Section 2.2 above, significant income-related differences are apparent among Canadians such that people living in poverty experience significantly poorer health and have a significantly shorter life expectancy indicating strong and consistent evidence of socio-economic disparities in health. The Public Health Agency of Canada (PHAC) reported in 2003 on CVD mortality rates in urban Canada noting age-standardized mortality rates due to ischemic heart disease were highest among those with the lowest income, more so for men than women.[270] More recently, citing data from 2007 PHAC reported[271] on social and economic disparities in CVD risk factors. They found that many risk factors were more common among men and women in the lowest income quintile and among those with less education compared to those in the highest income quintile and with more education, including smoking, physical inactivity during leisure time, inadequate consumption of vegetables and fruit, high blood pressure, and diabetes. The prevalence of diabetes was almost three times higher in the lowest income quintile, while the prevalence was about twice as high for daily smoking and self-reported high blood pressure. PHAC notes that many factors can contribute to this higher prevalence of CVD risk factors among individuals with low income and low education including a lack of knowledge about healthy behaviours, lack of access to healthy foods, which are often more expensive, and high levels of stress that can lead to unhealthy coping behaviours.

Experts on the social determinants of health have long challenged the notion that CVD risk factors, as described in the INTERHEART and INTERSTROKE studies, are "modifiable" or that they are separable from social living conditions. While both of these large studies recognize that some of the "modifiable" risk factors can be out of personal control, particularly stress, they also point to, but do not analyze, underlying social factors. In the literature on the social determinants of health, and in an attempt at a more holistic approach to describing underlying causes, the leading risk factors for CVD are noted as material deprivation, psychosocial stress and the adoption of unhealthy coping behaviours.[272] Within such a frame, the same risk factors are addressed but with

269 Rosengren A et al (2004) Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (the INTERHEART study): case-control study. *The Lancet*; 364:953-962.

270 Public Health Agency of Canada (2003) The Growing Burden of Heart Disease and Stroke in Canada, 2003.

271 Public Health Agency of Canada (2009) *Tracking Heart Disease and Stroke in Canada*. Chapter 3: The Genetic Epidemiology of Cardiovascular Disease.

272 Raphael D and Farrell ES (2002) Beyond medicine and lifestyle: addressing the societal determinants of cardiovascular disease in North America. *Leadership in Health Services*; 15(4);i-v.

different emphasis. For example, key behavioural and biomedical risk factors are observed as being highly influenced by poverty and resulting stress, a reality that PHAC also recognizes, as noted above. As well, within a focus on material deprivation, key issues about early life development and experience are addressed, particularly influences such as fetal nutrition, a risk factor that is also not specifically addressed in the INTERHEART or INTERSTROKE analyses. Such early life influences on cardiovascular and related diseases are discussed below followed by a discussion of the possible contribution of environmental contaminants to CVD burden.

9.2.3 Fetal Nutrition and Prenatal Maternal Stress

As noted in the discussion in Section 3.1.1 about the Developmental Origins of Health and Disease (DOHaD) the earliest and now strongest evidence of the DOHaD concept relates to CVD and its risk factors. Specifically, there is extensive epidemiological, clinical and experimental animal evidence of associations between fetal and neonatal under-nutrition and major risk factors (hypertension, insulin resistance and obesity) for CVD, diabetes and the metabolic syndrome in adult life.

An extensive review[273] of the literature on the developmental origins of the metabolic syndrome describes the molecular, cellular, metabolic, neuroendocrine and physiological adaptations to the early nutritional environment, (in particular where under-nutrition is characterized by a low protein diet), that result in permanent developmental changes in key tissues and organs contributing to pathological consequences in adult life. This review describes the epigenetic, structural and functional adaptive responses that result in permanent programming of cardiovascular and metabolic function as well as the role of the interaction between the pre- and post-natal environment in determining final health outcomes.

This review notes that while the DOHaD evidence is traditionally focused on the impacts from low fetal nutrition, high fetal nutrition is increasingly relevant as well. Although the epidemiological and experimental animal evidence is more limited, the review also describes studies indicating similar developmental impacts, with similar adult health implications, for situations of *high* fetal nutrition particularly where there is some nutritional *imbalance* such as from excess prenatal intake of carbohydrates, salt or fats combined with inadequate protein intake.

In addition to the strong evidence for the fetal origins of key risk factors for CVD and diabetes (adult hypertension, insulin resistance and dyslipidemia) related to either maternal undernutrition or placental insufficiency,[274] the effect of chronic stress is also highly relevant at micro and macro levels. At the cellular level, chronic stress manifests as inflammation and oxidative stress, leading to the biochemical changes and risk factors (hypertension, etc.) underlying CVD as well as diabetes and other conditions.[275] However, the more obvious experience of chronic life stress also affects cardiovascular health.

For example, in animal studies, increased levels of stress hormones are associated with deficits in nephron formation in the kidney and hypertension in the offspring.[276] (Nephrons are the basic structural unit in the kidney that, among other functions, regulate sodium levels in the blood.) These associations are seen experimentally via administration of synthetic glucocorticoids and application of stressors, resulting in elevated maternal corticosterone, the natural glucocorticoid. The authors note that increased levels of corticosterone may have important implications for women experiencing significant stress during pregnancy. Another commentator describes this study as being of major clinical importance since the levels of natural stress hormones in the study correspond to those seen under stress conditions in real life.[277] The further comment is made that, whereas fetal under-nutrition may not be a major issue in Western diets, good evidence exists that social stress during pregnancy is a growing problem. Examples noted include high numbers of

273 McMillen CI and Robinson JS (2005) Developmental Origins of the Metabolic Syndrome: Prediction, Plasticity, and Programming. *Physiological Reviews*; 85:571-633.

274 Barker DJP (2004) The developmental origins of adult disease. *Journal of the American College of Nutrition*; 23(6 Supple.):588S-595S.

275 Johnstone SE and Baylin SB (2010) Stress and the epigenetic landscape: a link to the pathobiology of human diseases? *Nature Reviews Genetics*; 11:806-812.

276 Singh RR et al (2007) Prenatal corticosterone exposure results in altered AT_1/AT_2, nephron deficit and hypertension in the rat offspring. *Journal of Physiology*; 579(2):503-513.

277 Hocher B (2007) Fetal programming of cardiovascular diseases in later life – mechanisms beyond maternal undernutrition. *Journal of Physiology*; 579(2):287-288.

women without a stable partnership or with no support from family members, the stress or fear of losing career opportunities, the uncertainty about the economic situation following delivery, etc. This author concludes that fetal programming of CVD induced by stress during pregnancy is likely to be a major health care issue in Western countries. [278]

A recent review[279,280] of animal studies looks at the role of the kidney in programming of hypertension and notes evidence of multiple impacts on perinatal kidney development including lower numbers of nephrons and several areas of dysregulation in the renin-angiotensin-aldosterone system (that is, the integrated systems linking the kidney, the cardiovascular system and the brain that comprise the biochemical mechanisms for the kidney's role in filtering the blood including maintaining sodium levels and regulating blood pressure).

Describing this DOHaD evidence is not meant to imply that the major risk factors for CVD are entirely developmental in origin. However, this evidence indicates that early life influences are significant and likely of greatest importance to those living in poverty both in terms of nutritional factors and stress. The experts who have developed the DOHaD concept in fact suggest that the epidemiological data provide support for renaming the metabolic syndrome as the "small baby syndrome."[281] Evidence extends the DOHaD concept to include the antecedents of the separate and combined pathologies of the metabolic syndrome (that is, the early origins of hypertension, insulin resistance, glucose intolerance, and obesity) as risk factors for CVD and type 2 diabetes.[282]

This evidence is highly relevant to understanding the combined roles of the social determinants of health (SDOH) and early environmental exposures in contributing to these same risk factors and to CVD. As noted in the previous section, a SDOH framing of CVD risk factors, with its focus on highlighting impacts from material deprivation, psychosocial stress and adoption of unhealthy coping behaviours,[283] is aligned with a DOHaD approach. All three SDOH-related risk factors for example, can contribute to poor maternal and thus fetal nutrition (whether from undernutrition or overnutrition where either are unbalanced and/or lacking in protein). The SDOH approach also serves to highlight the role of stress on health, including pre- and post-natal maternal stress. Additional research points to similar health consequences of stress during childhood. For example, a recent study[284] investigating the physiological impact of prolonged stress among children living in poverty found altered serum cortisol levels that might indicate an adaptive coping mechanism but that may also lead to chronic impacts on physical and mental health.

9.2.4 Environmental Risk Factors in Cardiovascular Disease – Adults

Although the traditional risk factors, as described in the INTERHEART and INTERSTROKE studies above, account for most of the heart disease risk in a population and are thus crucial risk factors to control, there is increasingly clear evidence of impacts on population level CVD from a number of environmental exposures as elaborated below.

9.2.4.1 Particulate Air Pollution

Particulate air pollution is notably absent from the CVD risk factors described in the INTERHEART analysis. This absence is noted in an extensive literature review into associations between CVD and particulate matter air pollution by the American Heart Association (AHA).[285] The AHA, while acknowledging the traditional risk factors, concluded that the overall evidence is consistent with a

278 See also: Seckl JR and Holmes MC (2007) Mechanisms of Disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nature Clinical Practice - Endocrinology and Metabolism*; 3(6):479-488.

279 Baum M (2010) Role of the kidney in the prenatal and early postnatal programming of hypertension. *American Journal of Physiology – Renal Physiology*; 298:F235-F247.

280 See also: Gardner DS et al (2007) Fetal Mechanisms That Lead to Later Life Hypertension. *Current Drug Targets*; 8:894-905.

281 Barker DJP et al (1993) Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidemia (syndrome X): relation to reduced fetal growth. *Diabetologia;* 36:62–67.

282 McMillen and Robinson (2005) *op cit*

283 Raphael and Farrell (2002) *op cit*.

284 Dulin-Keita A et al (2010) Do neighbourhoods matter? Neighbourhood disorder and long-term trends in serum cortisol levels. *Journal of Epidemiology and Community Health*; e-pub ahead of print, doi:10.1136/jech.2009.092676

285 Brook RD et al (2010) Particulate Matter Air Pollution and Cardiovascular Disease – An Update to the Scientific Statement From the American Heart Association. *Circulation*; 121:2331-2378.

causal relationship between $PM_{2.5}$ (fine particulate matter) exposure and cardiovascular morbidity and mortality.

This AHA review builds upon a previous comprehensive review of evidence[286] and reaches additional conclusions including: short term (a few hours up to a few weeks) increased $PM_{2.5}$ exposure triggers CVD and mortality; longer term exposure reduces life expectancy by several months to a few years among the more highly exposed in a population (notably, often those experiencing poverty[287,288]); lowering of exposure results in decreased CVD mortality within a short time frame (a few years); and credible pathological mechanisms are increasingly understood to make these findings plausible.

Like the AHA, the Canadian Medical Association (CMA) concurs that adequate scientific evidence exist for a causal relationship between exposure to air pollution and adverse health outcomes including CVD. Building upon this premise, in 2008 the CMA[289] published results of applying the Illness Costs of Air Pollution (ICAP) model that had been developed and previously applied by the Ontario Medical Association (OMA).[290] The ICAP model estimates the health effects and economic costs of air pollution. It is a conservative approach in that it includes only those health effects where strong evidence of associations exists. The title of the report (*No Breathing Room – the Illness Costs of Air Pollution*) tends to imply a primary focus on respiratory health outcomes. While high costs of respiratory illness and mortality are certainly the case, the majority of deaths and most of the calculated costs are related to CVD. Among the model predictions is the finding that 42% of acute premature deaths associated with air pollution will be as a result of CVD.

The above is a very brief summary of the considerable evidence available for air pollution risk factors in CVD among exposed *adults*, particularly the elderly, recognizing that much of the premature CVD mortality predicted in the CMA study is among those over age 65.

9.2.4.2 Lead

There is also strong evidence for links between lead exposure and CVD in adults. In a literature review[291] on this topic, the authors conclude that sufficient evidence exists to infer a causal relationship between low level lead exposure and hypertension and suggestive evidence (though not sufficient to infer causation) for a relationship with clinical cardiovascular outcomes and changes in heart rate variability.

Subjects across all of the studies reviewed (twelve in general populations and 18 in occupational settings) were above the age of eight and most were adults. In drawing their conclusions about a causal link with hypertension, the authors point to the need for more research to determine the precise dose-response relationship, the relative importance of short-term versus chronic exposures, greater understanding of relevant mechanisms (including nephrotoxicity among others) at environmental levels of exposure, and whether the magnitude of the association is different in children or other vulnerable population subgroups. While these studies do not confirm a relationship between early exposures and later life hypertension, multiple studies included measures of bone lead which, compared to measuring lead in blood, provide an indication of cumulative or chronic exposure.

These authors consider the evidence from this review to be of major public health significance. Given the finding of causal associations with hypertension in adults at blood lead levels at or below 5 µg/dl,[292] they note that this level is less than half the level considered to be of clinical

286 Brook RD et al (2004) Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*; 109:2655-2671.

287 Evans GW and Kantrowitz E (2002) Socioeconomic Status and Health: The Potential Role of Environmental Risk Exposure. *Annual Reviews of Public Health*; 23:303–31.

288 Finkelstein MM et al (2005) Environmental inequality and circulatory disease mortality gradients. *Journal of Epidemiology and Community Health*; 59:481–487.

289 Canadian Medical Association (2008) *No Breathing Room – National Illness Costs of Air Pollution*. Technical Report. ICAP Model Version 3.0: Provincial Models and National Damage Estimates

290 Ontario Medical Association (2005) *Illness cost of air pollution, 2005-2026 health and economic damage estimates*.

291 Navas-Acien A et al (2007) Lead Exposure and Cardiovascular Disease – A Systematic Review. *Environmental Health Perspectives;* 115(3):472-481.

292 As noted in Section 3.3.1, since the majority of scientific literature on lead reports blood-lead measures in micrograms per decilitre, the Canadian convention of metric nomenclature is not used in this report to describe blood-lead levels.

concern in terms of neurotoxic effects in children (as discussed further in Section 11.6 below). Note that recent biomonitoring data of the Canadian population indicate that blood-lead concentrations range between about one and four µg/dl[293] providing little to no safety margin for exposures of concern to cardiovascular health. Moreover, they point to evidence in another review[294] of epidemiological studies of renal function and lead-related nephrotoxicity at these same low exposure levels. Drawing upon multiple lines of evidence, these authors conclude that very low level lead exposure (below 5 µg/dl) acts alongside more established risk factors for chronic kidney disease and the rate of progression of the disease. While this review is of epidemiological studies in adults, the authors note that cumulative lead dose was associated with worse renal function. Such studies expand upon what has long been known about associations between lead exposure in adults at higher occupational levels of exposure and renal dysfunction and hypertension.[295] More limited evidence indicates that lead and cadmium, (as well as uranium, mercury, and halogenated hydrocarbons), may be toxic to the developing kidney. As well, this evidence indicates that renal impacts from exposure to toxic agents are similar in children and in adults, and may include hypertension, but more research is necessary.[296]

9.2.4.3 Bisphenol A

Finally, emerging evidence indicates a possible link between BPA and CVD. For example, in the National Health and Nutrition Examination Survey (NHANES) of a large and representative sample of the U.S. adult population, urinary BPA concentrations were associated with an increased prevalence of coronary heart disease among survey subjects. The study authors note the urgent need for studies to clarify the mechanisms for these associations.[297] (See Section 3.3.1 above for a discussion of BPA levels measured via biomonitoring in Canadians.) A previous cross-sectional study[298] found similar results. Higher urinary BPA concentrations were associated with more diagnoses of CVD and type 2 diabetes as well as abnormal concentrations of liver enzymes indicative of altered insulin signalling affecting both sugar and fat metabolism. They also found no association with other common health endpoints indicating specificity of the associations with CVD and type 2 diabetes.

9.2.5 Environmental Risk Factors in Cardiovascular Disease – Early Life

For early life exposures, the balance of this section considers the evidence for associations with congenital heart defects as well as those associated with outcomes of relevance to the DOHaD concept, notably low birth weight. Endocrine disruption is also considered since the developing cardiovascular system, like many other physiological systems of the body, is hormone sensitive and thus at risk from endocrine disrupting substances.

9.2.5.1 Cardiac Birth Defects

Birth defects in the heart are the most common of all birth defects, by a considerable margin, as noted in Section 9.1 above. Some can result in lifelong health concerns and can be risk factors for later life CVD such as pulmonary hypertension, blood clots, abnormal heart rhythm, etc.[299] The causes of birth defects (not reviewed in detail here) are not fully understood but are considered to be the result of a complex interplay between genetic and environmental factors (the latter very broadly defined to encompass nutrition, infection and contaminants).[300] However, for the purposes of this review, it is relevant to note that certain environmental exposures are associated with cardiac birth defects.

293 Statistics Canada (2010) Canadian Health Measures Survey: Cycle 1 Data Tables 2007 to 2009. Statistics Canada, Physical Health Measures Division, Catalogue no. 82-623-X

294 Ekong EB et al (2006) Lead-related nephrotoxicity: A review of the epidemiological evidence. *Kidney International*; 70;2074-2084.

295 Loghman-Adham M (1997) Renal Effects of Environmental and Occupational Lead Exposure: A Review. *Environmental Health Perspectives*; 105:928-938.

296 Solhaug MJ (2004) The Developing Kidney and Environmental Toxins. *Pediatrics*; 113(4):1084-1091.

297 Melzer D (2010) Association of Urinary Bisphenol A Concentration with Heart Disease: Evidence from NHANES 2003/06. *PLoS ONE*; 5:e8673.

298 Lang IA et al (2008) Association of urinary bisphenolA concentration with medical disorders and laboratory abnormalities in adults. *Journal of the American Medical Association*; 300:1303–1310.

299 American Heart Association (2010) The Impact of Congenital Heart Defects http://www.heart.org/HEARTORG/Conditions/CongenitalHeartDefects/TheImpactofCongenitalHeartDefects/The-Impact-of-Congenital-Heart-Defects_UCM_001218_Article.jsp

300 March of Dimes (2006) *Global Report on Birth Defects: The Hidden Toll of Dying and Disabled Children*.

For example, animal evidence links air pollution to a range of birth defects. Limited epidemiological evidence from highly polluted areas in Eastern Europe,[301] as well as a slightly less polluted area in southern California,[302] links cardiac birth defects to ambient air pollution, specifically exposure to carbon monoxide and ozone (itself a secondary pollutant generated by other air pollutants including nitrogen dioxide and hydrocarbons).

Evidence linking cardiac birth defects with chemical exposures is discussed in two detailed reviews, the first summarizing evidence of associations with numerous drugs, alcohol, and organic solvents found in dyes, lacquers and paints,[303] and the second, noting the increasingly stronger evidence, mainly occupational, for links to cardiac birth defects with exposure to organic solvents and chlorophenoxy herbicides.[304] Both reviews note evidence of associations between cardiac birth defects and specific solvents among the halogenated hydrocarbons, particularly trichloroethylene (TCE) and dichloroethylene (DCE), while a third comprehensive review[305] describes the animal and human data (both community and occupational exposures) linking TCE to cardiac birth defects. Both TCE and DCE may be present in some contaminated drinking water supplies. Additional drinking water contaminants associated in some studies with cardiac birth defects include disinfection byproducts, such as trihalomethanes, though results seeking to confirm these associations are inconsistent and meta-analyses do not support an association.[306] Additional studies provide evidence of associations between certain pesticides and cardiac birth defects.[307,308] Finally, evidence of associations with cardiac birth defects also exists for exposure to ionizing radiation, lead, and additional air contaminants including benzene, sulphur dioxide and second hand tobacco smoke.[309]

9.2.5.2 Low Birth Weight

Compared to environmental associations with cardiac birth defects, a much larger body of evidence indicates associations between a range of prenatal environmental exposures and impacts on preterm birth, length and weight at birth, and fetal growth including intrauterine growth retardation (IUGR).[310]

Within the DOHaD framework, there is very strong evidence that low birth weight (LBW) contributes to later life CVD, as described in Section 8.1 above. However, understanding of this link began with evidence of LBW relating to circumstances of maternal and fetal undernutrition and the subsequent understanding that a range of adaptive structural and functional responses in the fetus and infant can contribute to adult hypertension, insulin resistance and dyslipidemia, among other adverse effects. As this concept has developed, additional contributing factors have been identified, notably maternal stress.

It may not necessarily follow that contaminants that are associated with LBW, or similar adverse impacts on fetal growth, will have the same CVD consequences. Nevertheless, with such strong evidence of a link between LBW and later life CVD, where environmental exposures are associated with LBW, they should be cause for prudent concern in the context of risk factors for CVD (in addition to the many other adverse impacts of LBW, as noted in Section 8.1 above). Moreover,

301 Lewtas J (2007) Air pollution combustion emissions: Characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects. *Mutation Research*; 636: 95–133.
302 Ritz B et al (2002) Ambient Air Pollution and Risk of Birth Defects in Southern California. *American Journal of Epidemiology*; 155(10:17-25.
303 Mone SM et al (2004) Effects of Environmental Exposures on the Cardiovascular System: Prenatal Period Through Adolescence. *Pediatrics;* 113(4):1058-1069.
304 Stillerman KP et al (2008) Environmental Exposures and Adverse Pregnancy Outcomes: A Review of the Science. *Reproductive Sciences*; 15(7):631-650.
305 National Research Council (2006) *Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues*. Washington DC: National Academy Press..
306 Nieuwenhuijsen M et al (2008) Chlorination disinfection by-products and risk of congenital anomalies: Review and Meta-Analyses. *Environmental Health Perspectives*; 116(2):216-222.
307 Loffredo CA et al (2001) Association of Transposition of the Great Arteries in Infants with Maternal Exposures to Herbicides and Rodenticides. *American Journal of Epidemiology*; 153(6): 529-536.
308 Weselak M et al (2006) Pesticide Exposures and Developmental Outcomes: The Epidemiological Evidence. *Journal of Toxicology and Environmental Health*, Part B, Critical Reviews; 10(1):41-80.
309 Weinhold B (2009) Environmental Factors in Birth Defects: What We Need to Know. *Environmental Health Perspectives*; 117(10): A441-A445.
310 Wigle DT et al (2008) Epidemiologic evidence of relationships between reproductive and child health outcomes and environmental chemical contaminants. *Journal of Toxicology and Environmental Health B Critical Reviews*; 11:373-517.

LBW is also considered a "crude surrogate" for changes during development.[311] For example, in reviewing the DOHaD concept, nephrologists note[312] that altered organogenesis can occur without changes in birth weight and the kidney appears to be particularly vulnerable to the effects of sub-optimal maternal nutrition, and to maternal stress, as discussed above. Hence, similar concern is warranted for environmental exposures associated with impacts on the developing kidney, specifically where any are associated with reductions in nephron formation.

In two of the above-noted reviews[313,314] of the literature concerning links between environmental contaminants and adverse pregnancy outcomes, for impacts on fetal growth and length of gestation, not surprisingly, air pollution is again implicated. The authors point to the longstanding and instructive evidence linking maternal smoking with effects on reproduction, including preterm birth, and more recent evidence pointing to second hand or environmental tobacco smoke (ETS) as a risk factor. Like air pollution, tobacco smoke is a complex mixture of many of the same pollutants (e.g., PAHs, lead, cadmium) that arises from motor vehicles, industrial processes and other sources. For the CACs (described in Section 3.1.1) epidemiological evidence from several countries indicates associations between elevated exposures and greater risk of LBW and preterm delivery. Additional discussion about the evidence for these associations is contained in Section 13.2.3 below with respect to air pollution as a risk factor in LBW contributing to compromised lung development.

Also summarized in Section 13.2.3 below are additional literature reviews and individual studies investigating associations between preterm birth and environmental exposures. Section 13.2.3 describes the strength of evidence for associations between impaired fetal growth and exposure to CACs, particularly sulfur dioxide and particulates, as well as ETS, lead, mercury, OC and OP pesticides, nitrates in drinking water, arsenic, phthalates, brominated flame retardants, and polyfluorinated compounds (used as stain repellents). Across these many environmental risk factors for LBW or preterm birth, the evidence for air pollutants, including ETS, as well as for lead, is the most extensive.

9.2.5.3 Endocrine Disruption

Finally, endocrine disrupting substances, such as BPA, are of considerable interest in terms of links to CVD. Evidence of possible links between CVD and BPA exposure in adults are discussed above with indications of impacts on insulin signalling in the body thus affecting sugar and fat metabolism. Notably, evidence of effects on insulin metabolism is apparent in early life as well.

Animal evidence indicates that prenatal and perinatal exposure to BPA is associated with permanent alteration of insulin metabolism (the body's ability to metabolize sugars and fats), and thus is a potential risk factor for obesity[315,316] and metabolic syndrome,[317] which in turn can increase the risk for heart disease, cancer, diabetes and Alzheimer's disease as discussed further in subsequent sections below. Animal evidence also indicates that prenatal exposure to BPA and other androgen-like endocrine disrupting compounds are plausibly associated with polycystic ovarian syndrome (PCOS) in adult women, a condition which is in turn associated with increased lifetime risks for CVD and Type 2 diabetes.[318] Finally, animal evidence indicates an

311 Gluckman PD et al (2005) Lifelong echoes—A critical analysis of the developmental origins of adult disease model. *Biology of the Neonate*; 87:127–139.

312 Ingelfinger JR and Schnaper HW (2005) Frontiers in Nephrology: Perinatal Antecedents of Adult Disease. Renal Endowment: Developmental Origins of Adult Disease. *Journal of the American Society of Nephrology;* 16(9):2533-2536.

313 Stillerman KP et al (2008) Environmental Exposures and Adverse Pregnancy Outcomes: A Review of the Science. *Reproductive Sciences*; 15(7):631-650.

314 Lewtas J (2007) Air pollution combustion emissions: Characterization of causative agents and mechanisms associated with cancer, reproductive, and cardiovascular effects. *Mutation Research*; 636: 95–133.

315 Newbold RR et al (2007) Effects of endocrine disruptors on obesity. *International Journal of Andrology*; 31:201-208.

316 Somm E et al (2009) Perinatal Exposure to Bisphenol A Alters Early Adipogenesis in the Rat. *Environmental Health Perspectives*; 117:1549-1555.

317 Alonso-Magdalena P et al (2010) Bisphenol-A Exposure during Pregnancy Disrupts Glucose Homeostasis in Mothers and Adult Male Offspring. *Environmental Health Perspectives*; 118:1243–1250.

318 Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):293-342.

association between pre- and perinatal exposure to BPA[319] and phthalates,[320] and adult exposure to PCBs,[321] with lower testosterone levels in adult males. In turn, evidence is accumulating that low testosterone levels are a risk factor for CVD, diabetes and metabolic syndrome.[322]

Lead is also implicated in endocrine disruption since it is known to act on the hypothalamic-pituitary-adrenal (HPA) axis, that is, the neuroendocrine system that coordinates the body's physiological response to stress. Stress hormones also act on the HPA axis and animal research indicates lifetime consequences of combined maternal lead and stress.[323] While this evidence about lead and stress is focused on impacts on brain development, the authors note that dysfunction in the HPA axis has diverse physiological consequences. Indeed, investigations into the DOHaD concept point to disruption of the HPA axis as a key underlying mechanism linking early life events with later development of CVD and hypertension, metabolic disease such as obesity and diabetes, as well as other inflammatory-mediated diseases such as arthritis, among other chronic diseases.[324] Hence, the impact of lead exposure on the HPA axis is of relevance within the broader body of evidence supporting the DOHaD concept.

9.3 Early Exposures and Cardiovascular Disease – Key Points

- Despite a trend to dramatically decreasing rates of CVDs in Canada in past decades, the burden of CVD is expected to remain considerable, due to changes in demographics and underlying prevalence of risk factors.
- Heart disease and stroke, alongside cancer, remain the three leading causes of death and CVDs continue to be the leading cause of hospitalization in Canada.
- Canadian and international research indicates that nine significant biomedical and behavioural risk factors account for the vast majority (90% or more) of the population attributable risks for myocardial infarction (heart attack) and stroke.
- However, a social determinants of health approach indicates also that material deprivation, psychosocial stress and the adoption of unhealthy coping behaviours are critical underlying risk factors to consider, as is particulate air pollution and lifelong lead exposure.
- The DOHaD evidence indicates also that early life influences (including low fetal nutrition and nutritional imbalance) are highly significant and likely of greatest importance to those living in poverty both in terms of nutritional factors and stress.
- Although the traditional risk factors account for most of the heart disease risk in a population and are thus crucial risk factors to control, there is increasingly clear evidence of impacts on population level CVD from environmental exposures such as particulate air pollution and lead, and more limited evidence that other environmental exposures are also CVD risk factors.
- In addition to the CVD risk from low birth weight, congenital cardiac birth defects can also lead to later life CVD risk. These two outcomes are also associated with a wide variety of environmental exposures including air pollution and ETS, certain solvents, pesticides and heavy metals.
- Additional early life exposures that may contribute to later life CVD risk including substances with endocrine disrupting potential, like BPA and lead.

319 Richter CA (2007) *In vivo* effects of bisphenol A in laboratory rodent studies. *Reproductive Toxicology*; 24:199-224.

320 Hallmark N et al (2006) Effects of Monobutyl and Di(n-butyl) Phthalate *in vitro* on Steroidogenesis and Leydig Cell Aggregation in Fetal Testis Explants from the Rat: Comparison with Effects *in vivo* in the Fetal Rat and Neonatal Marmoset and *in vitro* in the Human. *Environmental Health Perspectives*; 115:390–396.

321 Goncharov A et al (2009) Lower Serum Testosterone Associated with Elevated Polychlorinated Biphenyl Concentrations in Native American Men. *Environmental Health Perspectives*; 117:1454–1460.

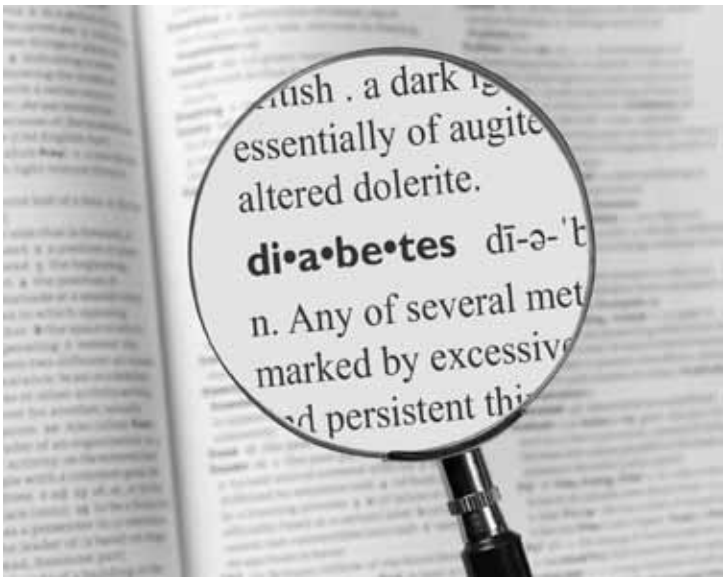
322 Jones TH (2010) Testosterone deficiency – a risk factor for cardiovascular disease? *Trends in Endocrinology and Metabolism*; 21(8):496-503.

323 Cory-Slechta DA et al (2008) Lifetime Consequences of Combined Maternal Lead and Stress. *Basic and Clinical Pharmacology and Toxicology*; 102:218-227.

324 Seckl JR and Holmes MC (2007) Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nature Clinical Practice Endocrinology and Metabolism*; 3(6):479-488.

10.0 Type 2 Diabetes

Diabetes is a chronic condition in which the body does not produce enough and/or does not properly use its own insulin, a hormone produced by the pancreas that enables cells to absorb glucose and transform it into energy. The result of reduced insulin secretion or effective action leads to chronic hyperglycaemia which in turn adversely affects how the body metabolizes carbohydrates, fats and proteins. Diabetes can lead to serious complications including multiple manifestations of CVD, as well as kidney failure, limb amputations, blindness, depression, and also to premature death.



10.1 Prevalence of Obesity and Diabetes

Of the two types of diabetes, Type 2 is the most common (generally about 90% of cases) and the focus of this discussion. Henceforth in this discussion diabetes is thus intended to mean Type 2 diabetes. As well, gestational diabetes may develop during pregnancy in non-diabetic women and create risks of obesity and diabetes in the offspring. Given the close association of diabetes with obesity, the following discussion also addresses obesity prevalence and risk factors in detail.

There is high prevalence and rising incidence of diabetes in Canada within the context of a global pandemic[325] of this disease. Global prevalence is expected to be close to 8% by 2030.[326] The Public Health Agency of Canada, through the National Diabetes Surveillance System, reports[327] the following statistics (current to 2007 and trends since 2002-03) on prevalence, incidence and related information profiling this disease among Canadians:

- Age-standardized prevalence of diagnosed diabetes increased by 21% from 2002-03 to 2006-07.
- In 2006-07, 6.2% of Canadians aged one year and older had diabetes. This number is equivalent to about 2 million people, or about 1 in every 16, with a prevalence of 5.9% among girls/women and 6.6% among boys or men.
- Projections for 2012 indicate that almost 2.8 million Canadians will be diabetic, an annual increase of about 6% and an overall increase of about 25% from 2007.
- Prevalence of diabetes varies in different provinces. The Ontario numbers have increased more than predicted for the national average. The rising diabetes prevalence in Ontario is most pronounced among young adults (age 20-49 years) and may be explained by rates of immigration from countries with populations with higher susceptibility to diabetes.[328]
- Incidence of newly diagnosed cases of diabetes in 2007 was 6.7 individuals per 1000 population aged one year and older with incidence in boys/men slightly more frequent than girls/women (7.3 compared to 6.1 per 1000 individuals). This increase is likely related to a corresponding increase in obesity and increased screening for diabetes.
- The age-standardized rate of new diabetes diagnoses increased almost 9% in the years

325 Wild S et al (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care;* (27):1047-1053.
326 Shaw JE et al (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Research and Clinical Practice*; 87(1):4-14.
327 Public Health Agency of Canada (2010) Report from the National Diabetes Surveillance System: Diabetes in Canada, 2009. On-line at: http://www.ndss.gc.ca
328 Lipscombe LL and Hux JE (2007) Trends in diabetes prevalence, incidence, and mortality in Ontario, Canada 1995-2005: a population-based study. *The Lancet*; (369):750-756.

between 2002-03 and 2007 while the age-standardized prevalence is increasing three times faster reflecting increased survival rates, particularly among those aged 40 to 69 years.

- Mortality rates among adults aged 20 and older are twice as high as among non-diabetics and a diabetes diagnosis significantly shortens life expectancy.
- Use of health services by diabetic individuals is dramatically higher than non-diabetics.
- Adults with diabetes, compared to non-diabetics, are three times more likely to have hypertension, heart attack or stroke, four times more likely to have heart failure, six times more likely to have chronic kidney disease and 19 times more likely to have lower limb amputations.
- Age-standardized prevalence of diagnosed diabetes among the First Nations population, aged one year or older, in British Columbia was about 40% higher than other BC residents.

Similarly high prevalence and rising incidence of diabetes exist among First Nations populations across Canada, where it is estimated that diabetes prevalence is three to five times higher than in the general population.[329,330,331]

The Public Health Agency of Canada also reports[332,333] on related information about obesity among Canadians:

- The prevalence of obesity (defined as a body mass index (BMI) of >30kg/m^2) among provinces and territories follows the same pattern as diabetes.
- Trend data indicate dramatically rising obesity rates with self-reported obesity typically lower than less-frequently available measured data with the result that the extent of obesity is underestimated.
- As of 2007, self-reported obesity among adults was 17% with the actual rate considered to be higher, likely around 25%.
- According to measured height and weight data from 2007-2009, over one in four Canadian adults (estimates range from 24.3% to 25.4%) are obese.
- In 2005, the measured rate for obesity among youth (age 12-17) was 9.4%, nearly twice the self-reported rate (4.9%).
- From more recent measured data from 2007-2009, among children and youth aged 6 to 17 years, 8.6% are obese.

The rising incidence of obesity among children is particularly striking. In 2004, more than one in four children in Canada aged 2 to 17 were overweight, including eight per cent who were classified as obese, with much higher levels among Aboriginal children.[334,335]

Prevalence of obesity and diabetes is known to be higher among people who are poor with data from the U.S. suggesting that the income-related gap in diabetes prevalence has widened over time.[336] Analysis of the Canadian Community Health Survey indicates that diabetes prevalence is over four times greater among the lowest income compared to the highest income Canadians with prevalence decreasing steadily with rising income. Moreover, the likelihood of diabetes was significantly higher for low-income groups even after adjusting for socio-demographic status,

329 Young TK (2000) Type 2 diabetes mellitus in Canada's first nations: status of an epidemic in progress. *Canadian Medical Association Journal*; (163):561-566.
330 Health Canada (2002) *Diabetes in Canada, Second Edition*.
331 Assembly of First Nations/First Nations Information Governance Committee (2007) First Nations Regional Longitudinal Health Survey (RHS) 2002-03 – Results for Adults, Youth and Children Living in First Nations Communities. Online at: http://www.rhs-ers.ca
332 Public Health Agency of Canada (2009) Obesity in Canada: Snapshot. On-line at: http://www.phac-aspc.gc.ca/publicat/2009/oc/pdf/oc-eng.pdf
333 Government of Canada (2011) *Obesity in Canada: A Joint Report from the Public Health Agency of Canada and the Canadian Institute for Health Information*.
334 Leitch KK (2007) *Reaching for the Top: A Report by the Advisor on Healthy Children and Youth*.
335 See also: Shields M (2006) Overweight and obesity among children and youth. *Health Reports*; 17(3):27-42. Statistics Canada, Catalogue 82-003.
336 Ross NA et al (2010) 14-year diabetes incidence: The role of socio-economic status. *Health Reports*; 21(3):19-28. Statistics Canada, Catalogue no. 82-003-XPE.

housing, body mass index and physical activity.[337] These and other risk factors are discussed in detail below.

Finally, data from the U.S.[338] and Canada[339] suggest a population-wide prevalence for metabolic syndrome at about 25%, roughly the same level suggested above for obesity in adults, with considerable variability across different ethnic (and likely also income) groups. However, agreement on a common definition for metabolic syndrome has only recently emerged[340] and was developed partly in response to the wide variability in prevalence data that resulted from previously varied definitions.[341]

10.2 Risk Factors for Obesity

The two most commonly recognized risk factors for obesity are excess food intake and insufficient physical activity, or an imbalance of "energy in and energy out." There is little doubt that these two factors can lead to overweight and obesity. However, a longer list of often interacting factors includes multiple circumstances that either contribute to each of these risk factors or are additional to them.

The trend in recent decades of excess caloric intake is recognized to be a result of dramatic changes in food manufacturing and marketing practices. These have included, for example, vending machines in schools, increased portion size in packaged foods and in restaurants, more frequent eating in restaurants, increased availability of inexpensive and energy-dense foods that often contain high levels of one or all of saturated fats, sugar and sodium, as well as the widespread use of high fructose corn syrup (also known as glucose/fructose) in inexpensive foods. Also in recent decades there has been a dramatic reduction in physical activity via more sedentary lifestyles, greatly increased time in front of televisions and computers, reduced school-based physical education and car-dependent urban design that discourages or subverts walking to accomplish basic daily tasks or routines. [342,343,344,345,346]

In a literature review[347] of factors contributing to the secular trend to increased obesity, obesity experts propose that public health interventions should expand beyond the disproportionate focus on these two main risk factors (excess food intake and reduced physical activity). While they do not dismiss the importance of both, they dispute the commonly held view that "obesogenic environments fostering low levels of physical activity and access to energy-rich diets are the most important determinants."[348] Rather, these reviewers note that evidence is both equivocal and largely circumstantial and point to the need to give more vigorous consideration to at least ten additional factors where the evidence is also incomplete but equally plausible.

The literature summarized in the above-noted review describes these ten additional factors to help explain the obesity epidemic as follows:

1. **Sleep debt** – Evidence from human studies, both cross-sectional and longitudinal, indicates that less sleep can cause increased body weight, animal evidence provides a mechanism of action, and additional data (U.S. residents but likely comparable to Canada) show that the average amount of sleep has steadily decreased in recent decades.

337 Dinca-Panaitescu S et al (2011) Diabetes prevalence and income: Results of the Canadian Community Health Survey. *Health Policy*; 99:116-123.
338 Biddinger SB and Kahn CR (2006) From mice to men: insights into the insulin resistance syndromes. *Annual Review of Physiology*; 68:123-158.
339 Anand SS et al (2003) Relationship of metabolic syndrome and fibrinolytic dysfunction to cardiovascular disease. *Circulation*; 108:420–425.
340 Alberti KG et al (2009) Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*; 120:1640-1645.
341 Alhassan S (2006) Metabolic Syndrome: Does Definition Determine Prevalence? *Circulation*; 114:II_873.
342 French SA (2001) Environmental influences on eating and physical activity. *Annual Review of Public Health*; 22:309–35.
343 Jeffery RW and Utter J (2003) The changing environment and population obesity in the United States. *Obesity Research*;11(Suppl):12S–22S.
344 Raine KD (2004) *Overweight and Obesity in Canada, A Population Health Perspective*. Ottawa: Canadian Population Health Initiative, Canadian Institute for Health Information.
345 Bray GA et al (2004) Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. *American Journal of Clinical Nutrition*; 79:537-543.
346 Maziak W et al (2007) Childhood obesity: are we missing the big picture? *Obesity Reviews*; 9:35-42.
347 Keith SW et al (2006) Putative contributors to the secular increase in obesity: exploring the roads less traveled. *International Journal of Obesity*; 30:1585-1594.
348 Unwin N et al (2010) Social determinants of diabetes and challenges of prevention. *The Lancet*; 375:2204-2205.

2. **Endocrine disruptors** – Evidence indicates humans have experienced increased exposure over at least the last three decades to multiple industrial chemicals that can affect endocrine function, specifically by increasing adiposity and via multiple mechanisms (as discussed in Section 9.2.4 and 9.2.5 above and in more detail below).
3. **Less variability in ambient temperature** – Extensive animal and human evidence confirms that temperature extremes, both hot and cold, will decrease adiposity while additional evidence confirms that far more people live in thermo-neutral conditions for most of their lives than was historically the case. Indeed, the highest obesity rates in the U.S. occur in the southern states and correlate with dramatic increases in the installation of central air conditioning since the 1970s.
4. **Decreased smoking** – Epidemiological and clinical evidence consistently show smokers weigh less than non-smokers and smoking rates have steadily decreased in recent decades though the reviewers hasten to add they are not suggesting a population-wide increase in smoking to address the obesity epidemic.
5. **Pharmaceutical iatrogenesis** – A large number of medications, for which use has increased dramatically in recent decades, are known to induce weight gain via activity at receptors involved in body weight regulation with these findings reproduced in animal models.
6. **Changes in distribution of ethnicity and age** – Evidence indicates that both older age and certain ethnicities are more prone to obesity. In both the U.S. and Canada demographic data indicate an aging population and increased frequency of ethnic groups with higher obesity prevalence, likely related to genetic predisposition.
7. **Increasing gravida age** – Epidemiological data, supported by studies in animals, indicate that having an older mother is a risk factor for obesity and gravida age is increasing globally creating a clinically meaningful ~7% increase in the odds of obesity.
8. **Intrauterine and intergenerational effects** – Epigenetic research indicates that extremes of energy imbalance *in utero*, either an excess or very limited caloric intake resulting in either high or low birth weight, can contribute to later life obesity and these effects may be transgenerational.
9. **Greater BMI associated with greater reproductive fitness yielding selection for obesity** – predisposing phenotypes – Human and animal evidence shows a strong genetic predisposition for greater body mass index (BMI) as well as greater fecundity among those with higher adiposity and/or obesity. This issue is discussed further below with respect to social determinants of obesity.
10. **Assortative mating and floor effects** – Evidence indicates that humans assortatively mate with those who are phenotypically similar (in this case overweight or obese). The result will be higher prevalence of obesity due to the known genetic component in adiposity and the fact that the historical definition of obesity was above the population median. As such, the floor for average weight is raised across the population and assortative mating does not have to have increased for it to have contributed to increasing obesity prevalence over time.

In drawing up this list, these reviewers further note a general inability to assign relative importance or measurable contributions of each. Some factors are more modifiable than others with obvious co-benefits (e.g., addressing sleep dept and excess use of air conditioning leading to healthier, more alert people using less fossil fuels) and usefully so; taking up smoking being an obvious choice to avoid. Several potential interconnections are noted among factors six through ten whereby genetic, epigenetic, population age distribution, age at pregnancy, and intergenerational effects may be jointly contributing to an overall trend towards greater obesity across the population.

The stated reasons for including these ten additional factors are that most are supported by a compelling body of evidence including ecological correlations, epidemiological evidence, supportive data from animal models, and strong theoretical or plausible mechanisms of action models. The authors consider that the available evidence plausibly links these factors to the obesity epidemic as convincingly as does the evidence supporting the contributions from excess

food intake and insufficient physical activity, and that they are thus worthy of greater attention and study.

Additional factors are noted that are supported by a more limited evidence base but, like the ten noted above, they include factors that have changed over the past thirty years. For example, human adenovirus 36 (AD-36) was first isolated as a new virus in 1978.[349] AD-36 is one of many viruses associated with respiratory and eye infections. Increased exposure since the early 1980s, (reflected in the presence of AD36-specific antibody in blood tests), has corresponded with the population-wide rise in obesity, particularly among children. Human AD-36 has been associated with increased body fat in several animal models and with obesity in cross-sectional human studies.[350,351] In children, not only were those who were AD36-positive more likely to be obese, their AD36-specific antibody status correlated with the severity of obesity.[352]

Yet another factor contributing to obesity is stress, a circumstance that few would argue has increased in recent decades, and that is known to be a significant issue for those living in poverty as discussed in Section 4 and Sections 9.2.2 and 9.2.3 above. Considerable evidence from both animal and human studies indicates that stress can induce overeating and obesity, particularly eating of so-called "comfort foods" typified by calorie-dense, high-fat or highly-sweetened fast foods.[353,354] Further, the involvement of the glucocorticoids (hormones involved in regulating glucose metabolism), insulin, and the brain's reward pathways supports the notion of food addictions providing a partial explanation for the limited success of lifestyle-focused programs and a suggestion to incorporate addiction response strategies in treatment and move away from approaches that blame the individual.[355]

Finally, the broad framing of these ten other obesity risk factors, in addition to Human AD-36 and stress, is useful for describing numerous evidence-informed influences on obesity that have changed in parallel with the roughly 30-year rising trend in population-wide obesity. However, this framing, (like most research into risk factors for obesity and diabetes),[356] includes relatively limited attention to the evidence concerning social determinants of obesity, including the disproportionate impact of social and psychosocial factors on those living in poverty. As noted in the preceding section, prevalence of obesity and diabetes is considerably higher among people living in poverty.

A review[357] of numerous observational and cross-sectional studies from multiple countries indicates that living in a low-income area is independently associated with obesity and poor diet. Contributing factors include more limited access to large supermarkets and greater access to fast food outlets compared to higher income areas. Additional differences include higher prices at small neighbourhood grocery stores that are less likely to stock healthy foods such as fruits and vegetables. These differences in food access are amplified by low income, absence of transport, (to shop and carry home groceries), and poor cooking skills or knowledge. While these associations have been found consistently in North America studies, results are more equivocal in other developed countries.

The above review of obesity risk factors is provided as an indication of two things. First, there is far more complexity involved than is generally implied when response strategies focus solely on individual behavioural changes in diet and physical activity. Second, a strong case exists in this evidence that other risk factors should be considered equally important in research and response strategies to obesity and, by extension, to obesity-related conditions including additional aspects of metabolic syndrome, diabetes, CVD, and Alzheimer's disease.

349 Wigand R et al (1980) New Human Adenovirus (Candidate Adenovirus 36), A Novel Member of Subgroup D. *Archives of Virology*; 64, 225-233.
350 Atkinson RL (2005) Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *International Journal of Obesity*; 29:281–286.
351 Atkinson RL (2007) Viruses as an etiology of obesity. *Mayo Clinic Proceedings*; 82(10):1192-1198.
352 Gabbert C et al (2010) Adenovirus 36 and Obesity in Children and Adolescents. *Pediatrics*; 126(4):721-726.
353 Dallman MF (2009) Stress-induced obesity and the emotional nervous system. *Trends in Endocrinology and Metabolism*; 23(3):159-165.
354 Puder JJ and Munsch S (2010) Psychological correlates of childhood obesity. *International Journal of Obesity*; 34:S37–S43.
355 Taylor VH et al (2009) The obesity epidemic: the role of addiction. *Canadian Medical Association Journal*; 182(4):327-328.
356 Chaufan C and Weitz R (2009) The Elephant in the Room: The Invisibility of Poverty in Research on Type 2 Diabetes. *Humanity and Society*; 33:74-98.
357 Cummins S and Macintyre S (2006) Food environments and obesity – neighbourhood or nation? *International Journal of Epidemiology*; 35:100-104,

For the sake of this analysis, these additional risk factors include 1) multiple aspects of the SDOH including, but not limited to, a food system that serves to promote excess intake of unhealthy food particularly among those living in poverty, and 2) exposure to endocrine disrupting substances, as discussed further below.

10.3 Diabetes and Other Chronic Diseases – Overlapping Risk Factors

Type 2 diabetes is typically described as resulting from a combination of genetic pre-disposition or susceptibility and environmental or lifestyle factors.

Genetic susceptibility to diabetes is complex and involves the same "non-modifiable" risk factors described in Section 9.2.2 above with respect to CVD and metabolic syndrome. Multiple genes are involved in influencing blood lipids and blood pressure and the likelihood that a person will be overweight, obese, develop insulin resistance or other disorders within the metabolic syndrome, or develop full diabetes. However, as discussed in Section 9.2.3 concerning fetal nutrition and maternal stress, early life epigenetic influences on later life disease risk must also be considered.

In addition to genetic risk factors, there is considerable overlap among the economic, social and psychosocial risk factors for obesity, metabolic syndrome, diabetes and CVD. As well, overweight and obesity are risk factors for diabetes, while all three are established risk factors for CVD itself, and for other CVD risk factors, such as hypertension.[358]

Obesity[359] and diabetes are both risk factors for multiple cancers[360,361,362] and for Alzheimer's disease,[363] cognitive impairment and dementia[364,365] (as is further discussed in Section 11 below). Obesity and diabetes in children are associated with subtle abnormalities in cardiovascular structure and function, likely increasing the risk of later life CVD.[366]

Finally and as a more specific subset of much of the above, those with metabolic syndrome (i.e., individuals with three out of five of: increased waist circumference, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure, and elevated fasting-glucose levels) are at high risk of CVD, type 2 diabetes, cancer and other diseases.[367]

Given these overlaps, the discussion of CVD risk factors in the previous section is frequently relevant to diabetes, including the INTERHEART and INTERSTROKE risk factors related to diet, physical activity, smoking, alcohol consumption, blood lipid levels, hypertension, abdominal obesity, and psychosocial stress. Also relevant to a discussion of diabetes risk factors is the extensive evidence of associations between fetal and neonatal under-nutrition in the context of the DOHaD concept discussed in Section 8.1.

10.3.1 Environmental Risk Factors in Adults

Similarly, for exposure to environmental contaminants, the evidence reviewed in Sections 9.2.4 above with respect to CVD in adults is relevant to diabetes risk where associations are apparent either directly with diabetes or with risk factors common to CVD and diabetes.

In addition, given that diabetes results from the induction of insulin resistance in the body alongside disruption of insulin-producing cells in the pancreas, investigations into effects of chemical substances are finding that diabetes is plausibly linked to exposures that appear to

358 The Emerging Risk Factors Collaboration (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *The Lancet*; 375:2215-2222.
359 Renehan AG et al (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*, 371(9612):569-78.
360 Renehan A et al (2010) Linking diabetes and cancer: a consensus on complexity. *The Lancet*; 375:2201-2202.
361 Mitri J et al (2008) Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care*; 31(12):2391-2397.
362 Giovannucci E et al (2010) Diabetes and Cancer, American Diabetes Association Consensus Report. *Diabetes Care*; 33:1674–1685.
363 Miller DB and O'Callaghan JP (2008) Do early-life insults contribute to the late-life development of Parkinson and Alzheimer diseases? *Metabolism Clinical and Experimental*; 57(Suppl 2);S44–S49
364 Roberts RO et al (2008) Association of Duration and Severity of Diabetes Mellitus with Mild Cognitive Impairment. *Archives of Neurology*; 65(8):1066-1073.
365 Sonnen JA et al (2009) Different Patterns of Cerebral Injury in Dementia With or Without Diabetes. *Archives of Neurology*; 66(3)315-322.
366 Berry C and Sattar N (2011) Stressed hearts in children with obesity and diabetes: a cause for concern? *Diabetologia*; 54:715-718.
367 Biddinger SB and Kahn CR (2006) From mice to men: insights into the insulin resistance syndromes. *Annual Review of Physiology*; 68:123-158.

disrupt both insulin metabolism and biochemical activity in the pancreas. A broad range of possible exposures and mechanisms of action are implicated in this disruption with evidence of effects in adults and more seriously during fetal and perinatal development.

10.3.1.1 Air Pollution

Within the AHA review (described in Section 9.2.4) of the evidence linking air pollution and CVD, impacts begin with systemic inflammation and oxidative stress. These conditions can then contribute to diabetes risk factors including elevated blood pressure, insulin resistance, and disorders in the blood lipids. While most of the studies reviewed by the AHA showed enhanced risk from air pollution among those who already had diabetes, limited epidemiological evidence indicated a relationship between air pollution and diabetes onset[368,369] and still other studies showed associations between air pollution and hypertension as well as greater vulnerability to air pollution among those with metabolic syndrome or who were obese.

10.3.1.2 Lead

For lead exposure the evidence about links to hypertension is also relevant. This evidence is mainly derived from studies in adults but also indicates effects resulting from lifelong or chronic exposure, thus pointing to the likely relevance of childhood exposures. As noted in Section 9.2.4, there is sufficient evidence linking very low level lead exposure and hypertension to be considered causal. Thus, by extension, low level lead exposure should prudently be considered a contributing risk factor for diabetes. Recall from Section 9.2.4 that low level lead exposure in this context refers to levels of 5 ug/dl or less, i.e., levels that are at or only slightly higher than what occur in the general population as indicated by biomonitoring data.

10.3.1.3 Bisphenol A and Phthalates

For BPA, the two epidemiological studies discussed in Section 9.2.4 suggest possible links to both CVD and diabetes. While a possible mechanism of action was not clear from these human studies, the results indicated altered insulin signalling. Studies in mice of several endocrine disrupting substances, including BPA, demonstrate that adult exposure produces insulin resistance and other metabolic alterations including disrupted pancreatic cell function.[370,371] Additional effects related to insulin are apparent in pregnant mice and offspring including altered glucose metabolism in dams and altered glucose homeostasis and endocrine pancreatic function in offspring, as discussed further below with respect to early life exposures. More limited evidence from cross-sectional epidemiological studies indicates positive associations between six phthalate metabolites and measures of obesity including body mass index and waist circumference,[372] and measures of insulin resistance, a marker of metabolic syndrome.[373]

10.3.1.4 Organophosphate Pesticides

In addition to the above substances as environmental exposure risk factors for CVD and diabetes, organophosphate (OP) pesticides are an additional concern. Although some OP pesticides have been increasingly restricted and/or withdrawn from use in recent years due to human health and environmental concerns, many OP pesticides continue to be commonly used and they are a significant source of human pesticide exposure. A literature review[374] of animal studies and human epidemiological data shows associations between exposure to several OP pesticides

368 See also: Pearson JF et al (2010) Association Between Fine Particulate Matter and Diabetes Prevalence in the U.S. *Diabetes Care;* 33:2196–2201.

369 See also: Krämer U et al (2010) Traffic-related Air Pollution and Incident Type 2 Diabetes: Results from the SALIA Cohort Study. *Environmental Health Perspectives*; 118:1273–1279.

370 Alonso-Magdalena P et al (2006) The estrogenic effect of bisphenol-A disrupts pancreatic β-cell function *in vivo* and induces insulin resistance. *Environmental Health Perspectives*; 114:106-112.

371 Ropero AB et al (2008) Bisphenol-A disruption of the endocrine pancreas and blood glucose homeostasis. *International Journal of Andrology*; 31:194-200.

372 Hatch EE et al (2010) Association of endocrine disruptors and obesity: perspectives from epidemiological studies. *International Journal of Andrology*; 33:324-332.

373 Stahlhut RW et al (2007) Concentrations of urinary phthalate metabolites are associated with increased weight circumference and insulin resistance in adult U.S. males. *Environmental Health Perspectives*; 115:876-882.

374 Rezg R et al (2010) Organophosphorous pesticides as food contaminants and type 2 diabetes: a review. *Trends in Food Science and Technology*; 21:345-357.

and both obesity and incident diabetes. The animal studies showing associations with obesity indicate a stronger relationship when exposure occurs during development. In discussing possible mechanisms of action this review notes that the evidence points to possible OP pesticide involvement in disruption of glucose metabolism, insulin resistance, insulin deficiency and dyslipidemia via a broad range of endocrine disrupting actions affecting various hormones as well as metabolic processes involved in maintaining blood glucose concentrations. While this review does not regard the findings as definitive evidence, it notes that the hypothesis raises serious implications in need of further research.

10.3.1.5 *Persistent Organic Pollutants (POPs)*

Also implicated in diabetes incidence in adults are the POPs including OC pesticides, PCBs and dioxins. Although many of these substances have been banned or dramatically restricted, their persistence and bioaccumulative properties means that they, or their metabolites, (such as DDE, the main metabolite of the pesticide DDT), continue to circulate in the environment. They also occur at higher levels in the fat of animals that are high on the food chain, particularly the aquatic food chain. As well, the interaction of the chemical properties of POPs with climatic processes results in the highest environmental levels in the arctic food chain.

Occupational exposure to both OP and OC pesticides is associated with incident diabetes,[375] as is gestational diabetes among similarly-exposed agricultural workers.[376] Similarly, analyses of NHANES data in the U.S. indicates a strong dose-response relationship between elevated exposure to several POPs and diabetes prevalence.[377,378] In a study of people that consume Great Lakes sport fish, known to contain elevated levels of POPs, an association was found between incident diabetes and exposure to DDE.[379] Likewise in results from a study in Swedish women, elevated serum DDE levels were found to be a risk factor for diabetes, a finding in accordance with several other cross-sectional studies of DDE and other POPs.[380] Another environment-wide association study (EWAS) looking at multiple risk factors for diabetes found a significant association between diabetes and exposure to PCBs and heptachlor, an OC pesticide.[381]

Across all of the studies discussed above, the authors refer to evidence about the ability of POPs to affect insulin metabolism and/or interfere with cells in the pancreas and thus influence insulin production.[382] Alongside the epidemiological evidence of associations between elevated POPs exposure and diabetes, experimental studies in animals provide supporting evidence that exposure to POPs that are commonly present in the food chain leads to insulin resistance and associated metabolic disorders.[383,384] This evidence is of particular importance among Aboriginal populations in Canada where prevalence of diabetes is three to five times higher than in the general population. Studies of Aboriginal populations in Canada find associations between elevated POPs exposure in fish and wild game and an elevated risk of diabetes.[385] They note as well that the evidence suggesting links between obesity and the endocrine disrupting properties of several POPs (discussed further below), alongside evidence of associations between high levels of

375 Montogomery MP et al (2008) Incident Diabetes and Pesticide Exposure among Licensed Pesticide Applicators: Agricultural Health Study, 1993-2003. *American Journal of Epidemiology*; 167(10):1235-1246.

376 Saldana TM et al (2007) Pesticide Exposure and Self-Reported Gestational Diabetes Melitus in the Agricultural Health Study. *Diabetes Care*; 30(3):529-534.

377 Lee D-H et al (2006) A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes. *Diabetes Care*; 29:1638-1644.

378 Everett CJ and Matheson EM (2010) Biomarkers of pesticide exposure and diabetes in the 1999-2004 National Health and Nutrition Examination Survey. *Environment International*; 36;398-401.

379 Turyk M et al (2009) Organochlorine Exposure and Incidence of Diabetes in a Cohort of Great Lakes Sport Fish Consumers. *Environmental Health Perspectives*; 117(7):1076-1082.

380 Rignell-Hydbom A et al (2009) Exposure to *p,p'*-DDE: A Risk Factor for Type 2 Diabetes. *PLoS ONE*; 4(10):e7503.

381 Patel CJ et al (2010) An Environment-Wide Association Study (AWAS) on Type 2 Diabetes Mellitus. *PLoS ONE*;5(5):e10746, 1-10.

382 See also: Hectors TLM et al (2011) Environmental pollutants and type 2 diabetes : a review of mechanisms that can disrupt beta cell function. *Diabetologia*; published online: 27 March 2011. DOI 10.1007/s00125-011-2109-5

383 Ruzzin J et al (2010) Persistent Organic Pollutant Exposure Leads to Insulin Resistance Syndrome. *Environmental Health Perspectives*; 118(4):465-471.

384 See also: Remillard RBJ and Bunce NJ (2002) Linking Dioxins to Diabetes: Epidemiology and Biological Plausibility. *Environmental Health Perspectives*; 110(9):853-858.

385 Philibert A et al (2009) An Exploratory Study of Diabetes in a First Nation Community with Respect to Serum Concentrations of *p,p'*-DDE and PCBs and Fish Consumption. *International Journal of Environmental and Public Health*; 6:3179-3189.

POPs exposure and diabetes in Aboriginal populations, points to the possibility that obesity itself may not be the chief risk factor for diabetes.[386]

Finally, a literature review[387] about endocrine disruptors in the etiology of diabetes discusses the importance and high prevalence of metabolic syndrome pointing out that although the cause of metabolic syndrome is not fully understood, insulin resistance is a central feature. This review further describes the three main theories that link obesity to insulin resistance: 1) that obesity is an inflammatory state; 2) the adipokine theory that considers adipose tissue as an endocrine organ; and 3) the adipose tissue expansion theory, based on the limited capacity of adipocytes to grow. Regardless of different theories, across all three insulin resistance is considered to be induced by signalling molecules in the blood either because they are released from adipose tissue or they are not taken up by adipocytes. Given the fact that several endocrine disrupting compounds, (i.e., most of those discussed in the preceding paragraphs), accumulate in adipose tissue and can induce insulin resistance, these authors consider that these substances must be considered as factors linking obesity and insulin resistance. They further note that epidemiological evidence indicates that it is common for obese adults to be metabolically healthy and also common for normal weight adults to be metabolically unhealthy leading to a conclusion that insulin resistance rather than obesity may be the better predictor of metabolic risk, particularly for development of diabetes. Hence they further conclude that sufficient scientific evidence exists to state that every endocrine disrupting compound able to produce insulin resistance at levels known to be circulating in human plasma (again, most of the substances discussed in this section) may be considered a risk factor for metabolic syndrome and diabetes, independent of its obesogenic potential and its accumulation in adipocytes. The issue of "obesogens" is discussed further below.

10.3.2 Early Life Exposures as Risk Factors for Obesity and Diabetes

The above-described evidence (of associations in adult humans or adult animals between chemical exposures and obesity or diabetes) has given rise to multiple studies in cell cultures and animals conducted mostly during the last ten years. Investigators have sought to further understand what have been mostly cross-sectional epidemiological results and provocative findings in animal studies, most of which have pointed to disruption of metabolic homeostasis through endocrine pathways with greater risk when exposure occurs *in utero* or perinatally.

During the same time, greater understanding has developed about epigenetic mechanisms underlying obesity, metabolic syndrome and diabetes, particularly the influence of early life within the DOHaD framework discussed in Sections 8.1, 9.2.3 and 9.2.5 above. For example, a literature review[388] of studies exploring epigenetic mechanisms in the development of diabetes describes multiple epigenetic changes that can occur if nutrition is inadequate during critical developmental periods *in utero*. These epigenetic changes permanently alter the expression of genes that are linked to the later development of diabetes including genes governing the development and functioning of the pancreas and metabolic processes involved in glucose regulation and insulin secretion.[389]

Further, as introduced in Section 8.1, the DOHaD framework began with a focus on the negative adult health consequences of fetal under-nutrition. However, high fetal nutrition, including maternal obesity, has become more prevalent in recent decades. Similar adult health implications are apparent but with notable differences with respect to obesity. Whereas fetal under-nutrition is associated with later life diabetes emerging after reproductive senescence, fetal over-nutrition results in a series of neuroendocrine responses that program fat cell development and appetite

386 Sharp D (2009) Environmental Toxins, a Potential Risk Factor for Diabetes Among Canadian Aboriginals. *International Journal of Circumpolar Health*; 68(4):316-326.

387 Alonso-Magdalena P et al (2011) Endocrine disruptors in the etiology of type 2 diabetes mellitus. *Nature Reviews Endocrinology*; Advance Online Publication. 5 April 2011; doi:10.1038/nrendo.2011.56

388 Pinney SE and Simmons RA (2009) Epigenetic mechanisms in the development of type 2 diabetes. *Trends in Endocrinology and Metabolism*; 21(4): 223-229.

389 See also: Jones RH and Ozanne SE (2008) Fetal programming of glucose-insulin metabolism. *Mollecular and Cellular Endocrinology*; 297:4-9.

regulation. The effect is seen in the development of obesity in late childhood and adolescence that may then contribute to an intergenerational cycle of obesity.[390,391]

10.3.2.1 Low Birth Weight

In the discussion in Section 9.2.5 about environmental exposures as risk factors for CVD, those exposures linked to low birth weight are relevant to diabetes, while the discussion of endocrine disrupting substances is particularly relevant. With respect to low birth weight, in light of the strong evidence within the DOHaD framework of links to multiple chronic diseases, particularly CVD and diabetes, several exposures are of concern. As the evidence related to these exposures is described in Section 9.2.5, only the exposures of concern are repeated here. Exposures linked to low birth weight include air pollution, tobacco smoke, lead, mercury, arsenic, OC and OP pesticides, nitrates in drinking water, phthalates, brominated flame retardants and polyfluorinated compounds.

10.3.2.2 Endocrine Disruption

For endocrine disrupting substances, again, Section 9.2.5 notes that emerging evidence from animal studies indicates associations between early life exposure and 1) altered insulin metabolism (BPA), 2) adult development of polycystic ovarian syndrome (BPA and other androgen-like endocrine disrupting compounds), 3) adult manifestation of lower testosterone levels (BPA, phthalates, and PCBs) and 4) impacts on the physiological response to stress from the combination of maternal stress and lead exposure. Across each of these areas, risk factors arise for some or all of obesity, metabolic syndrome, CVD and diabetes.

The concept of endocrine disrupting substances as obesogens is of particular importance and this research is discussed in more detail here.

Reviews of this evidence often begin by noting that adipose tissue is essentially endocrine tissue; it is also referred to as an endocrine organ.[392,393] Over the past twenty years, fat cells, or adipocytes, have been increasingly understood by endocrinologists to be much more than an inert place to store excess metabolic fuel. Rather, adipose tissue secretes multiple hormones and proteins involved in dynamically regulating diverse aspects of whole-body energy expenditure, appetite, food intake and metabolism. This hormone and protein signalling occurs between adipose tissue and the central nervous system, other organs in the body, including endocrine organs, and to maintain lipid homeostatis in the liver. Hence, this chemical signalling ensures that a balance exists for either the creation and accumulation, or the mobilization of lipids in adipose tissue, in response to changes in nutrient intake and caloric demands. Many of these signalling chemicals originating in adipose tissue also play significant roles during growth and differentiation and it is increasingly understood that endocrine signalling pathways are permanently established during perinatal development.[394]

Evidence also indicates that endocrine disrupting substances can influence the creation of fat cells or adipogenesis and thus obesity. For adult exposures, the epidemiological and animal evidence of these effects is discussed in the previous section. For early life exposures, the DOHaD framework is highly instructive. First, it provides extensive animal and human epidemiological evidence that perinatal nutrition can significantly change the developing organism or child with long term health consequences for the adult. Second, alongside the well-established evidence that the developing fetus or neonate is uniquely sensitive to chemical exposures, there is growing understanding that epigenetic changes involved in DOHaD effects are similarly apparent in the investigation of how endocrine disrupting chemicals can adversely affect perinatal development. Indeed, the fields of maternal nutrition and endocrine disruptor toxicology have independently

390 McMillen IC et al (2008) Developmental Origins of Adult Health and Disease: The Role of Periconceptional and Foetal Nutrition. MiniReview, *Basic and Clinical Pharmacology and Toxicology*; 102: 82-89.

391 See also: Reusens B et al (2007) Fetal Determinants of Type 2 Diabetes. *Current Drug Targets*; 8:935-941.

392 Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):293-342.

393 See also: Galic S et al (2010) Adipose tissue as an endocrine organ. *Molecular and Cellular Endocrinology*; 316(2):129-139

394 Newbold RR et al (2008) Effects of endocrine disruptors on obesity. *International Journal of Andrology*; 31:201-208.

provided numerous examples of perinatal factors altering the developing organism and leading to long-term effects in the adult.[395] In particular, a wide range of chemicals are suspected as endocrine disrupting compounds that act on genes during development in a manner that permanently affects the nature of adipose tissue and multiple metabolic processes in the body.

10.3.2.3 Obesogens

The term obesogen originated in work published in 2006 and was defined as "molecules that inappropriately regulate lipid metabolism and adipogenesis to promote obesity."[396] These molecules act through endocrine pathways. Investigating their effects has considerably broadened the concept of endocrine disruption, a relatively new concept in science that initially focused on compounds that could interfere with estrogen and androgen signalling and thus affect both male and female reproductive functions, (and that are also linked to cancers in reproductive/endocrine tissues, as discussed in Section 12.4 and 12.5 below). Since endocrine signalling governs all tissues and organs, particularly during development, the understanding of endocrine disruption is expanding to include a much wider range of effects. Obesogens or "metabolic disruptors" are described as a subset of endocrine disrupting compounds that can perturb metabolic signalling.[397]

In a review[398] of endocrine disrupting chemicals and obesity, a long and growing list of chemicals are noted as possible obesogens including:

- The drug diethylstilbesterol (DES) (Most endocrinologists consider that sufficient causal evidence indicates DES as a known obesogen.)
- BPA (used in polycarbonate plastics and to line most food cans). (BPA exhibits multiple toxicological characteristics that are very similar to DES.)
- Phthalates (in soft vinyl products and many cleaners and personal care products)
- Organotins (used in plastics and as pesticides)
- PBDEs (increasingly restricted and/or banned but used extensively as flame retardants in multiple consumer products and thus commonly found in house dust as well as throughout the food chain).
- Polyfluoroalkyl chemicals (used as stain repellents and in non-stick cooking pans and paper).
- OC pesticides (largely banned but environmentally persistent pesticides).
- PCBs (also banned but environmentally persistent industrial chemicals).

The above review notes that the evidence for obesogenic properties of these substances comes mainly from toxicological studies in animals while epidemiological evidence is more limited and at times inconsistent. Further, experts can identify multiple plausible targets of endocrine disruption affecting weight homeostasis. They note that a distinction should be drawn between non-developmental and *in utero* exposures as the latter may have quite different effects on endocrine signalling pathways.

Another literature review[399] of endocrine disruptors as obesogens describes evidence of multiple obesogenic effects that are suspected from environmental pollutants, several pharmaceuticals, and from food components such as phytoestrogens and the sweetening agent glycyrrhetinic acid. Obesogenic effects are suspected via diverse mechanisms as follows:

- Effects may be mediated by metabolic sensors, such as occur on nuclear or membrane hormone receptors with greater effects from fetal or early life exposures.

395 Newbold RR et al (2009) Environmental estrogens and obesity. *Molecular and Cellular Endocrinology*; 304(1-2):84-89.
396 Grun F and B Blumberg (2006) Environmental obesogens: organotins and endocrine disruption via nuclear receptor signalling. *Endocrinology*; 147(*Suppl* 6):S50-S55.
397 Casals-Casa C et al (2008) Interference of pollutants with PPARs: endocrine disruption meets metabolism. *International Journal of Obesity*; 32(*Suppl* 6):S53-S61.
398 Hatch EE et al (2010) Endocrine disrupting chemicals and obesity. *International Journal of Andrology*; 33:323-332.
399 Grun F and Blumberg B (2009) Endocrine disruptors as obesogens. *Molecular and Cellular Endocrinology*; 304:19-29.

- Effects may be mediated by sex steroid dysregulation with multiple animal studies indicating possible effects that also appear to depend on both timing of exposure and gender.
- Effects may result from endocrine disruptors interacting with central neuroendocrine signalling that controls the whole body response to daily nutritional fluctuations, including appetite control. One of several of these effects appears to be on thyroid gland regulation of metabolism, another area where greater vulnerability exists during development given the central role played in fetal development by hormones from the maternal thyroid gland.
- Further neuroendocrine effects are suspected within glucocorticoid hormone signalling. This hormone is present in virtually every cell of all vertebrate animals. It is centrally involved in stress responses, in regulating glucose metabolism, in multiple aspects of fetal development, and if elevated during pregnancy, it can adversely affect fetal development. Disruption of glucocorticoid signalling (from stress and undernutrition, and perhaps also from endocrine disrupting chemicals) can contribute to multiple aspects of the metabolic syndrome.

These authors note that the incomplete evidence about effects of endocrine disrupting chemicals should be viewed alongside the much stronger evidence base within the DOHaD framework wherein there is a better understanding of the long term negative consequences on metabolic functioning that can result from inadequate fetal nutrition and excess maternal stress. Moreover, the understanding that epigenetic processes occurring perinatally drive these long term health consequences, suggests that similar epigenetic processes are a plausible mechanism for amplifying several environmentally-induced factors that are giving rise to the suddenness of the current obesity epidemic. Hence, the obesogen hypothesis proposes that the metabolic changes induced by environmental chemicals (i.e., altered fat differentiation or function and the initiation or misregulation of homeostatic controls) are superimposed on current trends of excess food intake and limited physical activity.

These investigations involve highly complex biochemistry. The situation is made more complex for many reasons including greater vulnerability to exposures that occur during developmental windows, the latency of effects long after exposure has occurred, and effects that may differ between genders or be affected by genetic predisposition. Not only are multiple environmental exposures of concern but these substances are ubiquitous in the environment. Effects measured in animal studies occur at exceptionally low levels in line with well understood action of hormones of the human endocrine system. Hence, effects seen in animal studies or indicated in epidemiological data are often measurable at environmentally relevant exposure levels.

All reviewers emphasize that this field requires much more investigation, including via more compelling epidemiological data. However, it is noteworthy that endocrinologists[400] emphasize that endocrine disruption can occur along diverse pathways, (estrogenic, antiandrogenic, thyroid, diverse nuclear receptors and membranes, steroidogenic enzymes, neurotransmitters and systems, neuroendocrine signalling, etc.), that these pathways are highly conserved in wildlife and humans, and they can be modelled *in vitro* and *in vivo*. Moreover, they contend that strong evidence exists for adverse reproductive effects (infertility, malformations, cancers as a result of early life exposures) and that mounting evidence exists for effects on other endocrine systems, including thyroid, neuroendocrine, metabolic, as well as on insulin and glucose homeostatis.

10.4 Early Exposures and Diabetes – Key Points

- There is a high prevalence (6.2% among those ages one and older in 2006-07) and rising incidence of type 2 diabetes in Canada, within the context of a global pandemic of this disease. Rates of diabetes are higher in Ontario than compared to the Canadian national average and distinctly higher among First Nations populations across Canada.

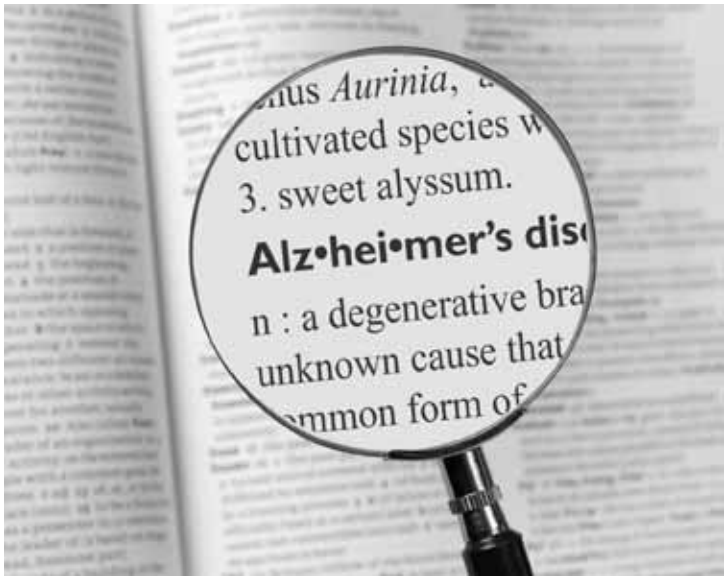
400 Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):293-342.

- Obesity is a clearly linked, independent risk factor for type 2 diabetes. The population statistics for diabetes are not surprisingly paralleled by dramatically rising obesity rates in Canada.
- Excess food intake and insufficient physical activity on a population level are still viewed as important contributors to the enduring trend to increasing obesity. However, experts indicate that several other risk factors, including exposure to endocrine disrupting chemicals, intrauterine environment and transgenerational factors, and social determinants of health (among others) provide plausible evidence of additional contributors to the global obesity pandemic.
- Alongside genetic risk factors, there is considerable overlap among the economic, social and psychosocial risk factors for obesity, metabolic syndrome, diabetes and CVD. In addition, obesity and diabetes are themselves risk factors for other chronic diseases such as CVD, certain cancers, Alzheimer's disease, cognitive impairment, and vascular dementia.
- A broad range of environmental exposures for which evidence suggests they may disrupt insulin metabolism or alter biochemical activity in the pancreas, are implicated in the onset of diabetes or of its related risk factors. Evidence is limited, largely cross-sectional in nature, and focussed on exposure during adulthood but has prompted studies in developing organisms that indicate endocrine disrupting compounds may act on genes during development in a manner that permanently affects the nature of adipose tissue and multiple metabolic processes in the body. These studies are instructive as to the possible associated diabetes risks from exposure to air pollution, lead, BPA, some phthalate metabolites, OP pesticides and POPs (such as DDE, PCBs and dioxins).
- The DOHaD framework and epigenetics contribute to understanding the role of intrauterine conditions (e.g. fetal undernutrition or overnutrition; low birth weight, exposure to endocrine-disrupting substances) in increasing risks for obesity and diabetes in later life.
- The concept of endocrine-disrupting substances as "obesogens," was first described in 2006. Suspected obesogens are typically ubiquitous environmental chemicals that may act at very low levels of exposure and inappropriately influence the creation of fat cells and permanently affect the nature of adipose tissue, metabolic processes in the body and weight homeostasis.
- This body of evidence is largely accumulating from toxicological studies. Epidemiological studies are more limited and less consistent in their findings of obesogenic properties of environmental chemicals. The list of possible obesogenic chemicals noted in recent reviews include DES, BPA, phthalates, organotins, PBDEs, polyfluoroalkyl chemicals, and POPs including OC pesticides and PCBs.
- Effects may occur by multiple mechanisms and may differ if exposure occurs *in utero* (during development) or after development is complete.
- The obesogen hypothesis proposes that the metabolic changes induced by environmental chemicals (i.e., altered fat differentiation or function and the initiation or misregulation of homeostatic controls) are superimposed on current trends of excess food intake and limited physical activity.
- This is an important area for further research, including a strong need for more compelling epidemiological data.

11.0 Impacts on the Brain – Focus on Alzheimer's and Parkinson's Disease

11.1 Introduction

Within CPCHE's focus on children's health, a high priority is placed on research, outreach and policy advocacy about substances that are known or suspected to be associated with impacts on the *developing* brain broadly including a wide range of effects on learning and/or behaviour. In contrast, within the chronic disease focus of OCDPA, attention is on neurodegenerative diseases and conditions in the *aging* brain: and specifically Alzheimer's disease (AD), other common forms of dementia including vascular dementia, as well as Parkinson's disease (PD). As well, OCDPA addresses issues of mental illness.



This section will focus on the aging brain, including prevalence data and risk factors for AD (with some consideration as well for vascular dementia) and PD. However, a summary is included of available prevalence data for neurodevelopmental and neurobehavioural disorders as well as a brief summary of key contaminants of concern where evidence exists of associations with impacts on the developing brain or developmental neurotoxicity. It is important to recognize that neurodevelopmental and neurobehavioural disorders can indeed be lifelong or chronic conditions. Unfortunately, the ability to include a more detailed review of associated risk factors was beyond an already large project scope.

11.2 Prevalence

11.2.1 *Prevalence of Alzheimer's Disease*

Alzheimer's disease (AD) is a neurodegenerative disorder that can include multiple changes in cognitive ability as a result of changes in areas of the brain controlling thought, memory and language. It is progressively debilitating with functional decline resulting in lost ability to live independently, progressing to death. The majority of those diagnosed with AD are over age 65.

In *Rising Tide: The Impact of Dementia on Canadian Society*,[401] the Alzheimer's Society of Canada provides data and projections for the incidence and prevalence of dementia. Referring to a rapidly growing "dementia epidemic" this report notes that approximately 500,000 people in Canada currently have AD or a related dementia and that number is predicted to be over 1.1 million by 2038. Dementia is the most significant cause of disability among Canadians over 65 years of age. AD represents approximately 63% of the dementias included in these data, projected to rise to 69% within 30 years. The second most common form is vascular dementia (accounting for about 20% of all dementias) and of relevance to this report since, like AD, it is on the same continuum of risk factors for CVD and diabetes discussed in previous sections. Worldwide, as with diabetes, a global pandemic is apparent with high prevalence (more than 35 million people living with dementia in 2010) and rising incidence such that by 2050 dementia is predicted to affect over 115 million people.[402]

401 Alzheimer Society of Canada (2010) *Rising Tide: The Impact of Dementia on Canadian Society.*
402 Alzheimer's Disease International (2010) World Alzheimer Report 2010: The Global Economic Impact of Dementia.

11.2.2 *Prevalence of Parkinson's Disease*

Parkinson's disease (PD) is also a progressively debilitating neurodegenerative disorder with a wide range of possible symptoms. It generally begins with symptoms that are movement-related including shaking or tremors, muscle stiffness or rigidity, slow movement and difficulty with walking and balance. It can also include depression, loss of sense of smell, changes in thinking ability, softer speech, stooped posture, and small handwriting. Cognitive and behavioural impacts are more common as the disease progresses.

In Canada, PD affects more than 100,000 people (or one out of every 100 adults) and eighty-five percent of those diagnosed are over the age of 65.[403] Given that the number of people over age 65 in Canada is predicted to rise dramatically over the next 30 years (11.6% to 23.6% of the population), PD incidence will likely increase significantly. PD prevalence in the world's ten most populous nations is predicted to double, to between 8.7 and 9.3 million people, by 2030.[404]

11.2.3 *Prevalence of Neurodevelopmental and Neurobehavioural Disorders*

In addition to the known evidence of harm to the developing brain from a small number of well-studied substances, and concern about many more (as summarized in Section 11.6 below), CPCHE's priority focus on the developing brain also derives from the fact that there appears to be a high prevalence and rising incidence among children in Canada of learning and behavioural problems even though limited trend data exist in Canada. During the 1990s, more than one quarter of children aged 6-11 years were affected by one or more identifiable learning or behavioural problem, according to data from the 1997 National Longitudinal Study of Children and Youth.[405] More recent data for learning disabilities indicate rising incidence among both children and adults. According to Statistics Canada, in 2006, 3.2 per cent of children aged 5 to 14 reported living with a learning disability and the number of Canadians aged 15 and over with learning disabilities rose by almost 40 per cent between 2001 and 2006.[406] Autism Spectrum Disorder is rising dramatically worldwide. According to Autism Canada, one in every 110 children is being diagnosed with autism today compared to 4.5 per 10,000 only 20 years ago.[407] In the U.S., autism in children rose by 57% between 2002 and 2006[408] and the role of environmental factors is being investigated.[409,410,411]

Multiple factors are involved in neurodevelopmental outcomes including genetics, socio-economic circumstances, etc., and a direct correlation is not implied here between environmental contaminants and learning disabilities, autism or other conditions in the developing brain. However, in a knowledge-based society, where children are routinely exposed to small levels of substances that are both known and suspected of developmental neurotoxicity (summarized in Section 11.6 below), these large numbers among children are very troubling. Sections 11.4 and 11.5 below discuss how some of the same substances of concern in the developing brain are also of concern for the aging brain, either directly or as risk factors for related conditions such as obesity, diabetes and CVD.

11.3 Neurodegeneration – A Continuum of Cognitive Decline with Mixed Pathologies

Although AD, vascular dementia, and PD are generally described as discrete conditions with prevalence data reported and/or estimated as described above, experts note that a continuum exists of numerous forms of neurodegeneration, each with associated symptoms and pathological

403 Health Canada and Parkinson Society Canada (2003) Parkinson's Disease: Social and Economic Impact. June, 2003.
404 Dorsey ER et al (2007) Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*; 68:384-386.
405 Landy S and Tam K (1998) Understanding the Contribution of Multiple Risk Factors on Child Development at Various Ages. Paper presented at Investing in Children. A National Research Conference. National Longitudinal Survey of Children and Youth. Ottawa, 27–29, October 1998.
406 Statistics Canada (2007) Participation and Activity Limitation Survey: 2006. *The Daily*, Monday, December 3, 2007.
407 Autism Canada Foundation (2009) *Annual Report*.
408 Rice C (2009) Prevalence of Autism Spectrum Disorders - Autism and Developmental Disabilities Monitoring Network, United States, 2006. *Morbidity and Mortality Weekly Report*; 58(SS10):1-20
409 Herbert MR (2006) Time to Get a Grip. Does an environmental role in autism make sense? How do we decide? *Autism Advocate;* Fifth edition, 45(5):18-25.
410 Adams JB et al (2009) The Severity of Autism Is Associated with Toxic Metal Body Burden and Red Blood Cell Glutathione Levels. *Journal of Toxicology*; Article ID 532640, doi:10.1155/2009/532640
411 Landrigan P (2010) What causes autism? Exploring the environmental contribution. *Current Opinion in Pediatrics*; 22:219-225.

markers. Hence, in addition to the symptoms of AD and PD described above, typical pathological markers include amyloid plaques and neurofibrillary tangles in the brains of AD patients, and loss of dopaminergic neurons in the substantia nigra as well as Lewy bodies in the brains of PD patients. For vascular dementia, pathological markers include vascular infarctions, atherosclerosis and other markers of vascular disease.[412]

However, research indicates a relatively poor correlation between such markers and clinical findings. Instead, there can be a spectrum of pathology with overlap between symptoms and pathological markers among diseases that are otherwise described as distinct.[413,414,415] Indeed, some experts note that mixed pathologies, that is, those found across various neurodegenerative conditions may be predictors of the degree of cognitive decline.[416] Notably, if a mix of pathologies is identified, particularly those associated with vascular disease, a broader range of prevention strategies are available given that major risk factors for CVD are well known and largely preventable.[417]

In particular, a key role underlying neurodegeneration is seen in the inter-related processes of inflammation and oxidative stress. Hence, an even broader continuum is apparent whereby later life neurodegeneration joins other chronic diseases and associated risk factors that are also linked to inflammation and oxidative stress, as discussed further below.

11.3.1 *Healthy Brain Development, Aging and Brain Reserve*

Another continuum to consider here is the lifelong course of healthy brain development and normal aging. Beginning very early in pregnancy, brain development continues until the end of adolescence. The normal aging process typically includes some cognitive decline late in life. A healthy brain throughout life is influenced by nutrition, exercise, genetics, and the many other interacting factors discussed below. Indeed, in a review[418] of early-life risk factors for AD, experts point to multiple lines of evidence suggesting that AD may originate in early life, both in terms of key risk factors and neuropathology.

The concept of brain reserve is central to whether, or when, AD or other forms of neurodegeneration manifest. Brain reserve refers to the brain's resilience and ability to cope with damage or decline, including the normal decline of aging, and also includes the notion of a threshold beyond which dementia or other forms of neurodegeneration occur. One of the first studies of this concept found many pathological markers of AD in people with no clinical symptoms.[419] The brain reserve is thought to be influenced by the multiple genetic, nutritional and other factors that will affect brain development such that less reserve exists where more risk factors are present that can lead to neurodegeneration, its earlier onset, or greater severity, than would otherwise occur. For example, a community-based case control study found an association between AD risk and the early-life childhood and adolescent environment. The authors noted that the areas of the brain that show the earliest signs of AD are the same areas that take the longest to mature during childhood and adolescence.[420]

Similarly for PD, a review[421] of early life influences notes that experts have long agreed that PD is likely a "threshold" disease such that clinical symptoms resulting from loss of dopaminergic

412 Stein J et al (2008) *Environmental Threats to Healthy Aging: With a CloserLook at Alzheimer's and Parkinson's diseases*. Chapter 3 – A Primer on Brain Structure and Function.
413 Langa KM et al (2004) Mixed dementia: emerging concepts and therapeutic implications. *Journal of the American Medical Association*; 292:2901-2908.
414 Prohovnik I et al (2006) Dissociation of neuropathology from severity of dementia in late-onset Alzheimer's disease. *Neurology*; 66:49-55.
415 Neuropathology Group of the Medical Research Council Congitive Function and Aging Study (MRC CFAS) (2001) Pathologic correlates of late onset dementia in a multicentre, community based population in England and Wales. *Lancet*; 357:169-175.
416 Schneider JA et al (2007) Mixed brain pathologies account for most dementia cases in community dwelling older persons. *Neurology*; 69:2197–2204.
417 Stein J et al (2008) *op. cit*. Chapter 5 – Classification Controversies in Neurodegenerative Disease.
418 Borenstein AR et al (2006) Early-Life Risk Factors for Alzheimer Disease. *Alzheimer Disease and Associated Disorders*; 20:63-72.
419 Katzman R et al (1988) Clinical, Pathological, and Neurochemical Changes in Dementia: A Subgroup with Preserved Mental Status and Numerous Neocortical Plaques. *Annals of Neurology*; 23:138-144.
420 Moceri VM et al (2000) Early-life risk factors and the development of Alzheimer's disease. *Neurology*; 54(2):415-420.
421 Barlow BK et al (2007) The gestational environment and Parkinson's disease: Evidence for neurodevelopmental origins of a neurodegenerative disorder. *Reproductive Toxicology*; 23:457-470.

function in the substantia nigra occur after many decades of effects from multiple environmental factors, including beginning early in life, that are persistent, cumulative and/or progressive. Included is the concept of "multiple hits" that are necessary before a PD threshold is reached and clinical symptoms occur.[422]

Also included in this concept is the notion of "silent toxicity" such that early insults *in utero* may occur in the brain from chemical exposures or secondary to influenza infection (occurring during pregnancy or in young adulthood) or more likely from multiple hit combinations of these and other risk factors. A wide range of animal evidence points to *in utero* insults creating epigenetic changes such that a state of "altered potential" is induced and maintained by altered gene expression with the hypothesized result of persistent and irreversible vulnerability to later disease, including greater vulnerability to disease risk factors.[423]

Applied to PD, while experts describe many outstanding challenges in epidemiological and toxicological research, nevertheless evidence suggests a key role for the gestational environment altering neurodevelopment and influencing later-life susceptibility to PD.[424] Hence, a healthy brain reserve is likely as important with PD as with AD.

Sections 11.4.6 and 11.5.5 below describe evidence linking certain early environmental exposures with AD and PD within these related concepts that arise from the DOHaD framework.

11.4 Alzheimer's Disease: Inter-related Risk Factors

Among the risk factors for AD (and often for vascular dementia as well), as with other chronic diseases there are non-modifiable and modifiable risk factors and multiple interactions among each.

The major health and lifestyle conditions involved as risk factors for AD include:[425]

- Diabetes
- Metabolic syndrome (or its individual components including obesity, hypertension and high cholesterol levels)
- CVD, including strokes and mini-strokes, as well as mild cognitive impairment
- Inadequate physical activity
- Unhealthy eating habits
- Stress and low socio-economic status.

Non-modifiable risk factors and the above modifiable risks are briefly discussed below, before addressing toxic substances. Additional risk factors not discussed further, include:

- Inadequate mental activity
- Low levels of formal education
- Previous head trauma
- Down Syndrome
- Chronic inflammatory conditions (including certain forms of arthritis)
- A history of clinical depression.

422 Cory-Slechta DA (2005) Studying Toxicants as Single Chemicals: Does this Strategy Adequately Identify Neurotoxic Risk? *Neurotoxicology*; 26:491-510.

423 Heindel JJ (2008) Animal Models for Probing the Developmental Basis of Disease and Dysfunction Paradigm. *Basic & Clinical Pharmacology & Toxicology*; 102:76–81.

424 Barlow BK et al (2007) *op cit*.

425 Diamond J (2008) *A Report on Alzheimer's Disease and Current Research*. Alzheimer Society of Canada.

11.4.1 *Advancing Age, Gender*

Advancing age is the most important risk factor. While dementia is not necessarily the normal condition of the aging brain, risk increases sharply among the elderly particularly among those over the ages of 75 and 80 years. Twice as many women as men get AD which appears to be related to living longer, on average, than men, their greater likelihood for diabetes, and mainly due to lower estrogen levels in the post-menopausal state. Despite being predominantly diseases of the elderly, emerging evidence also points to the involvement of early life factors, including the DOHAD concept and exposure to toxic substances, as discussed further in Section 11.4.6 below.

11.4.2 *Genetics*

Genetic risk factors are involved in AD in ways that are not fully understood but that very likely interact with other modifiable risk factors. There are specific mutated genes involved in early-onset AD (generally before the age of 60) or familial AD which comprise about 4 to 6% of all AD cases.[426] There are no known genetic causes for the more common, late-onset, and sporadic form of AD but experts agree that the presence of the ApoE4 (apolipoprotein E4) gene increases AD risk.[427] This gene is involved in synthesis of a protein involved in lipid transport and processing in the blood and the brain. This protein also clears amyloid-beta from the brain, another protein that is regularly cleared from all cells in the body and, if not cleared from the aging brain, can accumulate and form amyloid plaques, one of the pathological markers of AD. In a meta-analysis, investigators found a 3-fold greater risk of AD in carriers of one copy of this gene and a 15-fold greater risk where two copies were present.[428]

However, a large body of observational and longitudinal epidemiological research points to complex gene-environment interactions and gene-gene-diet interactions for ApoE4.[429] The implication of this research is that AD risk in those carrying ApoE4 is strongly influenced by multiple environmental factors including physical inactivity, drinking alcohol, smoking, and a diet high in saturated fats and low in polyunsaturated fats. It also appears to be influenced by lifelong lead exposure, and perhaps to exposure to other toxic substances, as discussed further below.

11.4.3 *Diabetes, Obesity, Metabolic Syndrome and Cardiovascular Disease*

Considerable evidence links diabetes and CVD, and their associated risk factors, on a continuum with AD, dementia and cognitive decline.[430,431,432,433] One review notes that several large prospective studies estimate that relative to non-diabetics, people with diabetes have increased risk of AD and vascular dementia.[434] Similarly, extensive evidence, though some conflicting,[435] indicates associations between elevated dementia risk and obesity,[436] diabetes and other components of the metabolic syndrome,[437 438] as well as hypertension and other vascular risk factors in CVD.[439,440] Multiple complex mechanisms are apparent that may link these conditions and diseases with AD

426 Munoz DG et al (2000) Causes of Alzheimer's disease. *Canadian Medical Association Journal*; 162(1): 65-72.
427 Butler AW et al (2009) Meta-analysis of linkage studies for Alzheimer's disease – A web resource. *Neurobiology of Aging*; 30:1037–1047.
428 Farrer LA et al (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease – A meta-analysis. *Journal of the American Medical Association*; 278:1349-1356.
429 As reviewed in Stein J et al (2008) *op. cit.* Chapter 7: Environmental Factors in the Development of Dementia: Focus on Alzheimer's Disease and Cognitive Decline.
430 Bourdel-Marchasson I et al (2010) Review: Insulin resistance, diabetes and cognitive function: Consequences for preventative strategies. *Diabetes and Metabolism*; 36:173–181.
431 Pasquier F et al (2006) Review - Diabetes mellitus and dementia. *Diabetes and Metabolism* ; 32:403-414.
432 See also: Stein J et al (2008) *op. cit.* Chapter 7: Environmental Factors in the Development of Dementia: Focus on Alzheimer's Disease and Cognitive Decline.
433 Craft S (2009) The Role of Metabolic Disorders in Alzheimer Disease and Vascular Dementia – Two Roads Converged. *Archives of Neurology*; 66(3):300-305.
434 Biessels GJ et al (2006) Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurology*; 5(1):64-74.
435 Daviglus ML et al (2011) Risk Factors and Preventive Interventions for Alzheimer Disease - State of the Science. *Archives of Neurology*; Published online May 9, 2011 doi:10.1001/archneurol.2011.100
436 Gustafson D (2006) Adiposity indices and dementia. *Lancet Neurology*; 5(8):713-720.
437 Frisardi V et al (2010) Metabolic-cognitive syndrome: A cross-talk between metabolic syndrome and Alzheimer's disease. *Ageing Research Reviews;* 9(4):399-417.
438 Kivipelto M et al (2005) Obesity and Vascular Risk Factors at Midlife and the Risk of Dementia and Alzheimer Disease. *Archives of Neurology*; 62:1556-1560.
439 Duron E and Hanon O (2008) Hypertension, cognitive decline and dementia. *Archives of Cardiovascular Diseases;* 101:181–189.
440 Li J et al (2011) Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. *Neurology*; 76:1485-1491.

and vascular dementia and this discussion is, of necessity, greatly simplified (but is included for the sake of further discussion of links to environmental exposures, continued below).

Disrupted insulin signalling as a result of inflammation and oxidative stress appears to be of particular importance. As discussed with respect to risk factors for CVD and diabetes, inflammation in the body is seen via biochemical markers indicating activity in the immune system, for example in response to excess saturated fats in the diet or the release of hormones and related compounds from adipose tissue. Chronic diseases including diabetes, atherosclerosis and CVD, are typically referred to as chronic inflammatory diseases. Oxidative stress, a related metabolic state, is seen in elevated levels in the body of reactive and unstable oxygen compounds ("free radicals" or Reactive Oxygen Species – ROS). Both processes also occur in the brain, they tend to increase in the aging brain, and both are key features of AD and vascular dementia. Indeed, within, and in addition to, the evidence cited above of associations between dementia and obesity, diabetes, or other chronic diseases, multiple prospective population-based studies[441,442,443,444,445,446] indicate that an increase in one or more inflammatory markers in the blood constitutes a distinct risk factor for cognitive decline or dementia. Finally, both inflammation and oxidative stress are known to be linked to key risk factors for chronic disease including poor nutrition, inadequate exercise, obesity, as well as air pollution[447,448] and some other chemical exposures (as discussed further below).[449]

Disruption of insulin signalling resulting from inflammation and oxidative stress leads to multiple impacts including:

- Abnormally elevated blood sugar (negatively affecting the kidneys, brain, cardiovascular system, causing increased fat synthesis in the liver, etc.)
- Abnormally elevated levels of lipoproteins and triglycerides in the blood (adversely affecting movement of fats and cholesterol in the bloodstream).
- Disruption of nitric oxide production in blood vessel linings (reducing flexibility of arteries and veins in the heart, brain and peripheral arteries).

All of these impacts, or their biological or pathological markers, tend to be present or worsened in the metabolic syndrome, diabetes, hyperlipidemia, hypertension and CVD. Considerable evidence places AD and vascular dementia on this continuum due to shared biochemical features (as described above) between AD and diabetes, such as impaired insulin signalling and deposition of insoluble protein aggregates,[450,451,452] as well as other inflammatory processes involved in AD.[453] It is not surprising therefore that disruption of insulin, (the key metabolic hormone affecting the entire body), as well as obesity/excess adipose tissue, (the latter being the body's largest endocrine organ), will affect all body systems, particularly the brain. Some researchers consider Alzheimer's a neuro-endocrine disorder and have even proposed the term, "type 3 diabetes" or "diabetes of the brain" as a mechanism of neurodegeneration.[454,455]

441 See studies cited in the previous paragraph.
442 See also: Yaffe K et al (2004) Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology*; 63:658-663.
443 See also: van Oijen M et al (2008) Fasting insulin levels and cognitive decline in older women without diabetes. *Neuroepidemiology*; 30:174-9.
444 See also: Okereke OI et al (2008) Plasma C-peptide levels and rates of cognitive decline in older, community-dwelling women without diabetes. *Psychoneuroendocrinology*; 33(4)455-61.
445 See also: Irie F et al (2008) Enhanced risk for Alzheimer disease in persons with type 2 diabetes and apoE4. *Archives of Neurology*; 65:89-93.
446 See also: Lovestone S (1999) Diabetes and dementia: is the brain another site of end-organ damage? *Neurology*; 53:1907.
447 Delfino RJ et al (2010) Association of Biomarkers of Systemic Inflammation with Organic Components and Source Tracers in Quasi-Ultrafine Particles. *Environmental Health Perspectives*; 118:756-762.
448 Delfino RJ et al (2008) Circulating Biomarkers of Inflammation, Antioxidant Activity, and Platelet Activation Are Associated with Primary Combustion Aerosols in Subjects with Coronary Artery Disease. *Environmental Health Perspectives*; 116:898-906.
449 As reviewed in Stein J et al (2008) *op. cit.* Chapter 6: Underlying Dimensions of Neurodegenerative Disease.
450 Lee Y-H et al (2008) Amyloid Precursor Protein Expression Is Upregulated in Adipocytes in Obesity. *Obesity*; 16:1493-1500.
451 Merlo S et al (2010) Alzheimer's disease: brain expression of a metabolic disorder? *Trends in Endocrinology and Metabolism;* 21:537–544.
452 Helzner EP et al (2009) Contribution of Vascular Risk Factors to the Progression of Alzheimer's Disease. *Archives of Neurology*; 66(3):343-348.
453 Skaper, SD (2007) The Brain as Target for Inflammatory Processes and Neuroprotective Strategies. *Annals of the New York Academy of Sciences*; 1122:23-34.
454 Rivera EJ et al (2005) Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *Journal of Alzheimer's Disease*; 8:247–268.
455 Moreira PI et al (2007) Brain mitochondrial dysfunction as a link between Alzheimer's disease and diabetes. *Journal of the Neurological Sciences;* 257:206–214

11.4.4 *Poverty, Stress, Physical Activity and Nutrition*

As discussed throughout this report, socio-economic status is a strong predictor of health and those living in poverty are much more likely to be afflicted with chronic disease. Insofar as this trend extends to AD and other forms of dementia, those affected by these health conditions are extremely vulnerable and high cost and unique challenges are involved in caring for them. Also raised in previous discussions, poverty, social isolation, inadequate access to nutritious food, and high levels of stress tend to occur together. Lack of physical activity,[456] excess stress,[457] and poor nutrition[458] (including high glycemic carbohydrates, excess saturated fats, and deficient levels of essential omega 3 fatty acids and micronutrients) are all known to create excess (i.e., to "upregulate") inflammation and oxidative stress in the body. Indeed, the negative effects of stress and poor diet in combination are thought to be more than additive.[459]

11.4.5 *Environmental Contaminants – Adult Exposures*

11.4.5.1 *Recap of Obesity, Diabetes and CVD Environmental Exposure Risk Factors*

Evidence of associations between adult exposures to toxic substances and AD is briefly reviewed here. Insofar as a continuum is apparent (as discussed above) whereby AD shares common risk factors with obesity and other components of the metabolic syndrome, diabetes and CVD, it is reasonable to state that known or suspected environmental risks for these other conditions or diseases are also shared.

To summarize, as described in Section 9.2.4, evidence indicates that adult exposures to air pollution, lead, and bisphenol A are risk factors for CVD. The discussion in Section 10.3.1 about diabetes and obesity notes these same exposures as risk factors for adults and adds phthalates, OP pesticides, and POPs. However, noting this continuum is not meant to imply that a similar body of evidence demonstrates direct associations between these exposures and AD. Rather, these environmental exposures associated with obesity, diabetes or CVD in adults are generally involved in up-regulating inflammation and/or oxidative stress, and thus may also be risk factors for AD. More specifically, the following three sub-sections briefly summarize evidence of associations more directly between AD and three areas of environmental exposures among adults.

11.4.5.2 *Lead*

In prospective studies of those occupationally exposed to lead, results suggest that lead may have made a significant contribution to "normal" age-related cognitive decline.[460] Earlier work[461] by these researchers noted that the persistent effect of lead on the central nervous system may be more toxic in those carrying the ApoE4 gene (the genetic risk factor for AD discussed in Section 11.4.2 above) while other research found that a history of toxic exposure (toxic substances unspecified but investigations done across various occupations) significantly lowered the age of onset for cognitive decline. These researchers state that this effect was equivalent in magnitude to carrying two copies of the ApoE4 gene.[462] For environmentally exposed adults, additional longitudinal

456 Nicklas BJ et al (2005) Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. *Canadian Medical Association Journal*; 172(9):1199-1209.
457 Kiecolt-Glaser JK et al (2007) Depressive Symptoms, omega-6:omega-3 Fatty Acids, and Inflammation in Older Adults. *Psychosomatic Medicine*; 69:217–224.
458 Cordain L (et al) 2005 Origins and evolution of the Western diet: health implications for the 21st century. *American Journal of Clinical Nutrition*; 81:341–54.
459 Kiecolt-Glaser JK (2010) Stress, Food, and Inflammation: Psychoneuroimmunology and Nutrition at the Cutting Edge. *Psychosomatic Medicine*; 72:365-369.
460 Stewart WF and Schwartz BS (2007) Effects of Lead on the Adult Brain: A 15-Year Exploration. *American Journal of Industrial Medicine*; 50:729-739.
461 Stewart WF et al (2002) ApoE Genotype, Past Adult Lead Exposure, and Neurobehavioural Function. *Environmental Health Perspectives*; 110(5):501-505.
462 Schmechel DE et al (2006) Strategies for dissecting genetic-environmental interactions in neurodegenerative disorders. *Neurotoxicology*; 27;637-657.

research[463,464,465] indicates that cumulative lead exposure may also contribute to steeper than normal rates of cognitive decline in the elderly.

Additional evidence in one of these non-occupationally-exposed cohorts (the U.S. Veteran Affairs Normative Aging Study) points to an interactive effect with stress such that combined lead exposure and stress modify the relationship between age and cognition.[466] Given that higher levels of both stress and lead exposure are known to occur among those living in low socio-economic circumstances, these authors note that these findings may have significant public health implications. Moreover, as this research has continued to indicate effects on cognitive decline from chronic exposure to environmental levels of lead, it has also addressed whether early life exposures may also be important, as discussed further in Section 11.4.6.3 below.

11.4.5.3 *Air Pollution*

A series of studies has been conducted in Mexico City investigating the neurodegenerative effects in dogs and people of heavily polluted air. An early study in dogs suggested that the effects of persistent pulmonary inflammation and deteriorating olfactory and respiratory barriers may be involved in neuropathology.[467] While effects were measured in adult animals, this research pointed to the possibility that air-pollution related neurodegenerative effects such as AD might begin in early life. Another study found evidence of associations between exposure to severe air pollution and brain inflammation as well as accumulation in the brain of β-amyloid, both precursors to the neuronal dysfunction and pathological markers seen in AD.[468] This team also reviewed the literature of results from human subjects affected by AD, and multiple animal studies, concluding that when fine and ultrafine particles enter the blood stream from the lungs they disperse to multiple organs including the brain with the potential for neurodegenerative consequences, likely via oxidative stress pathways.[469] The work of this multi-national team (drawing from researchers in the U.S., Canada, Mexico and Chile) has continued to explore these effects in children and young adults, as discussed further in Section 11.4.6.2 below.

11.4.5.4 *PCBs*

Finally, there is some limited and/or emerging evidence of associations between PCBs and AD or dementia/cognitive decline.[470] Limited epidemiologic evidence from varied exposure circumstances (an accident causing contamination and poisoning, consumption of Great Lakes fish, and occupational exposure) indicate an association between AD and adult exposure to PCBs.

11.4.6 *Early Life Exposures and Alzheimer's Disease*

As noted above for adults, also relevant to early life exposures is the apparent continuum of disease, including shared risk factors for: obesity, metabolic syndrome, diabetes, CVD and AD.

11.4.6.1 *Recap of Obesity, Diabetes and CVD Environmental Exposure Risk Factors*

Previous sections summarize links between early life exposures and CVD (Section 9.2.5) and obesity and diabetes (Section 10.3.2).

463 Weuve J et al (2008) Cumulative Exposure to Lead in Relation to Cognitive Function in Older Women. *Environmental Health Perspectives*; 117(4)574-580.

464 Weisskopf MG et al (2004) Cumulative Lead Exposure and Prospective Change in Cognition among Elderly Men – The VA Normative Aging Study. *American Journal of Epidemiology*; 160(12):1184-1193.

465 Shih RA et al (2007) Cumulative Lead Dose and Cognitive Function in Adults: A Review of Studies That Measured Both Blood Lead and Bone Lead. *Environmental Health Perspectives*; 115(3):483-492.

466 Peters JL et al (2010) Interaction of Stress, Lead Burden, and Age on Cognition in Older Men: The VA Normative Aging Study. *Environmental Health Perspectives*; 118(4):505-510.

467 Calderón-Garcidueñas L et al (2002) Air Pollution and Brain Damage. *Toxicological Pathology*; 30(3):373-389.

468 Calderón-Garcidueñas L et al (2004) Brain Inflammation and Alzheimer's-Like Pathology in Individuals Exposed to Severe Air Pollution. *Toxicological Pathology*; 32:650-658.

469 Peters A et al (2006) Translocation and potential neurological effects of fine and ultrafine particles – a critical update. *Particle and Fibre Toxicology*; 3:13. doi:10.11.86/1743-8977-3-13.

470 As reviewed in Stein J et al (2008) *op. cit*. Chapter 7: Environmental Factors in the Development of Dementia: Focus on Alzheimer's Disease and Cognitive Decline and Chapter 8: Environmental Factors in the Development of Parkinson's Disease.

For CVD, exposures of concern are described that may be associated with cardiac birth defects, low birth weight, and endocrine disruption where each of these may influence later life CVD or its risk factors, particularly altered insulin signalling and related neuroendocrine signalling. As discussed in Section 9.2.5 these exposures included:

- For cardiac birth defects: air pollution, organic solvents, chlorophenoxy herbicides, trihalomethanes, additional pesticides, ionizing radiation, lead, and ETS.
- For low birth weight: air pollution, maternal smoking, lead, mercury, OC and OP pesticides, nitrates in drinking water, arsenic, phthalates, BFRs, and polyfluorinated compounds.
- For endocrine disruption: BPA, phthalates and lead.

For obesity and diabetes, in addition to those exposures noted above with respect to low birth weight, several endocrine disrupting substances are suspected as obesogens, as described in Section 10.3.2, including the drug DES, BPA, phthalates, organotins, PBDEs, polyfluoroalkyl chemicals, OC pesticides, and PCBs.

It is important to emphasize that direct links between these exposures and various forms of neurodegeneration is not meant or implied by creating the above summary. Rather, each should be considered in light of the strength of evidence discussed in these earlier sections and the evidence for a continuum of inter-related risk factors for multiple conditions and diseases, including AD.

11.4.6.2 Air Pollution

In ongoing work, described above, with respect to brain impacts as a result of adult exposures to high levels of air pollution in Mexico City, more recent results point to sub-clinical pathology beginning in childhood and among young adults. In a review,[471] this research team noted that, like the dogs and adults previously studied, healthy children had the same multiple markers of respiratory and systemic inflammation, including inflammation capable of reaching the brain, and systemic circulation of particulate matter. The dog studies, including very young animals, had brain inflammation and early markers of AD-like pathology.

Additional work by this team has found high air pollution associated with immunodysregulation and systemic inflammation in children[472] and also with neuroinflammation/neurodegeneration in healthy children and young adults who died suddenly (mostly due to accidents).[473] These latter findings included multiple markers in the brain of neuroinflammation and oxidative stress, disruption of the blood-brain barrier, deposition in the brain of ultrafine particles, and accumulation in the brain of amyloid β-42 and β-synuclein, both precursor components of the amyloid plaques seen in the brains of those with AD.

These researchers conclude that long term exposure to air pollution should be considered a risk factor for both AD and PD and note further that carriers of the ApoE4 gene could have a higher risk if they live in a polluted environment providing further evidence of the likelihood of gene-environment interactions in complex chronic diseases.

11.4.6.3 Lead

Alongside the well-known adverse effects of lead on neurodevelopment, emerging research indicates a plausible link between early life lead exposure and AD. This research sits within a broader context of the "LEARn" (Latent Early-life Associated Regulation) model which posits integration of environmental risk factors and a developmental basis for AD.[474] It derives from the

471 Calderón-Garcidueñas L et al (2007) Pediatric Respiratory and Systemic Effects of Chronic Air Pollution Exposure: Nose, Lung, Heart, and Brain Pathology. *Toxicological Pathology*; 35:154-162.

472 Calderón-Garcidueñas L et al (2009) Immunotoxicity and Environment: Immunodysregulation and Systemic Inflammation in Children. *Toxicological Pathology*; 37:161-169.

473 Calderón-Garcidueñas L et al (2008) Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adults *Toxicological Pathology*; 36:289-310.

474 Lahiri DK and Maloney B 92010) The "LEARn" (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of Alzheimer's disease, and proposes remedial steps. *Experimental Gerontology*; 45:291-296.

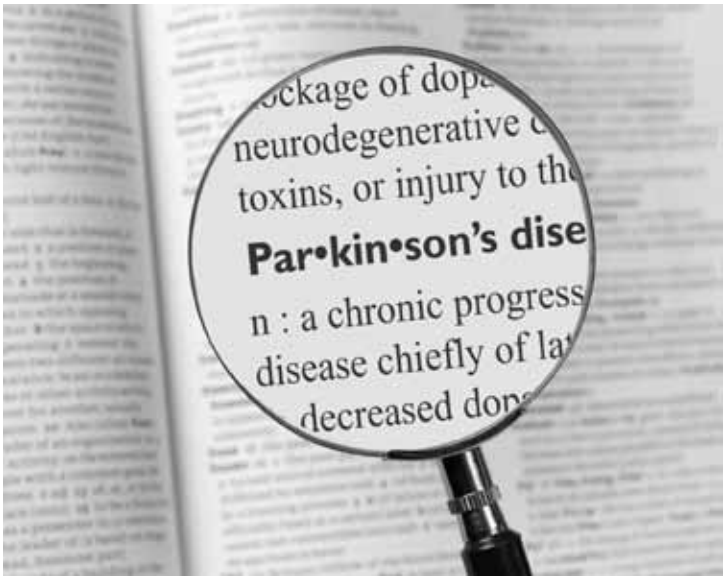
understanding that genetic factors are clearly involved in familial AD but cannot account for the majority of sporadic cases, these also being the type that are on the rise worldwide. Rather, early-life influences, including exposure to metals such as lead, as well as nutritional imbalance, poor maternal care, and other stressors influence the latent expression of AD-associated genes via epigenetic mechanisms. Such LEARn-modified genes require additional "triggers" or "hits" before pathology manifests, similar to the multiple hit concept raised by PD researchers, as described in Section 11.3.1 above.

The LEAR-n model originates from researchers who have studied early-life lead exposure in rodents and primates. These studies indicate associations between early life lead exposure and latent increase (i.e., in old age) in the brain of three biochemical precursors of AD including amyloid precursor protein (APP), amyloid β, and elevated 8-oxo-dG (a marker of oxidative DNA damage in the brain), long after the lead exposure has ceased.[475]

Epigenetic mechanisms appear to be involved such that environmental influences during brain development lead to changes in gene expression in response to gene-environment interactions. To summarize and simplify a very complex situation of brain biochemistry, this research indicates that expression of the gene that encodes for APP appears to be enhanced by early life exposure to lead with the result being latent increases in APP and amyloid β and the latter resulting in elevated production of ROS that can damage DNA (hence the biomarker of oxidative DNA damage). Additional epigenetic changes appear to repress other genes involved in DNA repair thus worsening the effects of oxidative DNA damage caused by excess amyloid β. While the link between lead and these effects is not certain, it is increasingly clear that a complex interplay of environment, epigenetics and oxidative stress may be at play in creating early life susceptibility to latent occurrence of AD.[476]

Limited human data indicate similar effects. In newborns in Mexico, an inverse association was found between cumulative lead measures (in bone) in mothers and similar epigenetic changes (as those found in the rodents and primates above) suggesting epigenetic imprinting that could influence later development of disease such as AD.[477]

11.5 Parkinson's Disease Risk Factors



As noted above, PD is a neurodegenerative disease resulting from the death of dopamine producing neurons in the substantia nigra, the area of the brain that helps to control movement. Dopamine carries signals between nerves cells in the brain and as these dopaminergic neurons die, the symptoms of PD appear. Although PD etiology is not fully understood, a complex situation is apparent of interactions between underlying genetic susceptibility with environmental factors in the context of normal aging. As well, evidence points to the likelihood of lifelong influences, within the "multiple hit" model described in Section 11.3.1 above. As with AD and other chronic diseases, risk factors include a similar situation of non-modifiable (age, gender, genetics) and modifiable (environmental) risk factors with multiple interactions.

475 Wu J et al (2008) The Environment, Epigenetics and Amyloidogenesis. *Journal of Molecular Neuroscience*; 34:1-7.
476 Zawia NH at el (2009) Epigenetics, oxidative stress, and Alzheimer's disease. *Free Radical Biology and Medicine*; 46:1241-1249.
477 Pilsner JR et al (2009) Influence of Prenatal Lead Exposure on Genomic Methylation of Cord Blood DNA. *Environmental Health Perspectives*; 117(9):1466-1471.

11.5.1 *Advancing Age and Gender*

Advancing age is the most important risk factor and men are at greater risk than women. Prevalence data indicate that PD occurs in men nearly twice as often though it is unclear if this is related to differential exposures to environmental risk factors.[478]

11.5.2 *Complex Gene-Environment Interactions*

For genetic risk factors experts conclude from results of several longitudinal and cross-sectional studies of twins that there appears to be a specific genetic component in a small number of PD cases (about 5% of cases and typically with early onset – before age 50) and a more general genetic susceptibility in a larger segment of the human population, likely via interaction with environmental triggers.[479] Other experts estimate that about 10% of PD cases are secondary to single-gene disorders with the remainder of cases due to an interacting mixture of genetic and environmental influences with the relative role of each likely different from individual to individual.[480] In a meta-analysis of genome-wide association studies, experts "[confirm] a strong genetic component" in PD but do not specifically quantify it and recognize the interplay with environmental factors.[481]

The combination of genetic and environmental factors underlying PD is apparent in a cross-sectional study of US Medicare beneficiaries.[482,483] In analysing over 450,000 PD cases, these investigators found PD to be substantially more common among White men, compared to Blacks and Asians, pointing to underlying genetic susceptibility, and a non-random distribution in the Midwest and North-eastern US, pointing to suspected environmental factors including exposure to pesticides and industrial pollution (discussed further below).

Ongoing uncertainty exists about putative roles and relative importance of specific genes or genetic pathways leading to PD. Two genome-wide association studies indicate the involvement in PD of many genes and extensive heterogeneity therein. For example, a very large number of genes have been identified for familial PD and variants of and/or damage to these genes have been identified[484] as being associated with sporadic PD. Included are genes that code for immune system function, lending support to the involvement of neuroinflammation as a causative factor in PD.[485]

As discussed in Section 11.3 above with respect to AD, the processes of chronic inflammation and oxidative stress both occur in the brain, they tend to increase in the aging brain, and both are suspected to play a role in the pathogenesis of PD, particularly oxidative stress.[486] Inflammation and oxidative stress,[487] as well as obesity,[488] (itself independently associated with markers of oxidative stress), also appear to be implicated in PD, although associations with obesity are inconsistent.[489,490,491]

478 Van Den Eeden et al (2003) Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity. *American Journal of Epidemiology*; 157(11):1015-1022.

479 Wirdefeldt K et al (2011) Heritability of Parkinson disease in Swedish twins: a longitudinal study. *Neurobiology of Aging* doi:10.1016/j.neurobiolaging.2011.02.017

480 Oliveira SA and Vance JM (2007) Genetic Risk Factors for Parkinson's Disease. Chapter 11 In: Dawson TM (ed) *Parkinson's Disease: Genetics and Pathogenesis*. New York : Informa Healthcare

481 International Parkinson Disease Genomic Consortium (2011) Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. *The Lancet*; 377:641-649.

482 Wright Willis A et al (2009) Geographic and Ethnic Variation in Parkinson Disease: A Population-Based Study of US Medicare Beneficiaries. *Neuroepidemiology*; 34:143-151.

483 See also: Van Den Eeden SK et al (2003) Incidence of Parkinson's Disease: Variation by Age, Gender, and Race/Ethnicity. *American Journal of Epidemiology*; 157(11):1015–1022.

484 Moran LB and Graeber MB (2008) Towards a pathway definition of Parkinson's disease: a complex disorder with links to cancer, diabetes and inflammation. *Neurogenetics;* 9:1–13.

485 Hamza TH et al (2010) Common genetic variation in the *HLA* region is associated with late-onset sporadic Parkinson's disease. *Nature Genetics*; 42(9):781-786.

486 Dauer W and Przedborski S (2003) Parkinson's Disease: Mechanisms and Models. *Neuron*; 39: 889- 909.

487 Whitton PS (2007) Inflammation as a causative factor in the aetiology of Parkinson's disease. *British Journal of Pharmacology*; 150:963–976.

488 Aitlhadj L et al (2010) Environmental Exposure, Obesity, and Parkinson's Disease: Lessons from Fat and Old Worms. *Environmental Health Perspectives*; 119:20–28.

489 Abbott R et al (2002) Midlife adiposity and the future risk of Parkinson's disease. *Neurology*; 59(7):1051-1057.

490 Chen H et al (2004) Obesity and the risk of Parkinson's disease. *American Journal of Epidemiology*; 159(6):547-555.

491 Hu G et al (2006) Body mass index and the risk of Parkinson disease. *Neurology*; 67(11):1955-1959.

PD typically includes oxidative stress in the brain combined with the loss of catecholamine hormones, particularly dopamine and norepinephrine.[492] These latter compounds act as hormones and neurotransmitters in the nervous and circulatory systems, dopamine with many different functions in the brain and norepinephrine involved in stress responses, in bringing oxygen to the brain, and in suppressing neuroinflammation. Oxidative stress in the brain is seen as playing a role in the development and progression of PD (particularly in the dopamine-producing area of the substantia nigra) but there is uncertainty as to whether it is a cause or consequence of the disease.[493] However, as discussed further below, for the environmental exposures linked to PD, virtually all involve increased oxidative stress.

Other mechanisms beyond oxidative stress are also involved in PD (including neuroinflammation and mitochondrial dysfunction, among others).[494] Though this discussion is greatly simplified and focused on oxidative stress, it is included for the sake of further discussion of links to environmental exposures, continued below.

11.5.3 *Poverty, Stress, Physical Activity and Nutrition*

Again, as previously discussed, socio-economic status is a strong predictor of health and those living in poverty are known to experience higher rates of chronic disease than people of higher socio-economic status. Also raised in previous discussions with respect to CVD, obesity, diabetes and AD, lack of physical activity, excess stress, and poor nutrition are all known to create excess inflammation and oxidative stress with the negative effects of stress and poor diet likely being more than additive.[495] A literature review into whether nutritional factors influence PD risk notes challenges in finding associations across many variables and limited prospective studies focused on this question. Some results point to possible neuroprotective effects of a combination of reduced caloric intake of predominantly healthy foods.[496]

11.5.4 *Environmental Contaminants – Adult Exposures*

11.5.4.1 *Recap of Obesity and Related Environmental Exposure Risk Factors*

As noted for AD, insofar as a continuum may exist whereby PD shares common risk factors with obesity or other conditions that include excess inflammation or oxidative stress, it is conceivable that known or suspected environmental risks for these other conditions or diseases are also shared.

To summarize, as described in Section 3.3 about diabetes and obesity, adult exposures to air pollution, lead, BPA, phthalates, OP pesticides, and POPs are risk factors for obesity and diabetes. For those that are specifically risk factors for obesity, they may also be relevant to PD. As noted for AD, noting this continuum is not meant to imply that a similar body of evidence demonstrates associations between these exposures and PD. Rather, these environmental exposures associated with obesity, diabetes (or CVD) in adults are generally involved in up-regulating inflammation and/or oxidative stress, and thus may also be risk factors for PD. More specifically, the following sub-sections briefly summarize where there is evidence of associations more directly between PD and specific environmental exposures among adults.

11.5.4.2 *Lead, Air Pollution*

Compared to AD, there is more limited evidence of associations between chronic exposure to lead and PD.[497] Likewise for the studies of associations between heavily polluted air and neurodegeneration described in Section 11.4.5.3 above, these investigators conclude that their

492 Surendran S and Rajasankar S (2010) Parkinson's disease: oxidative stress and therapeutic approaches. *Neurological Science*; 31:531–540.
493 Moran and Graeber (2008) *op. cit.*
494 Kanthasamy A et al (2010) Novel cell death signaling pathways in neurotoxicity models of dopaminergic degeneration: Relevance to oxidative stress and neuroinflammation in Parkinson's disease. *Neurotoxicology*; 31:555–561.
495 See multiple citations in Section 11.4.4 above.
496 Gaenslen A et al (2008) Nutrition and the risk for Parkinson's disease: review of the literature. *Journal of Neural Transmission*; 115:703-713.
497 Weisskopf MG et al (2010) Association of Cumulative Lead Exposure with Parkinson's Disease. *Environmental Health Perspectives*; 118(11):1609-1613.

results are relevant to both AD and PD with the potential for neurodegenerative consequences, likely via the oxidative stress pathway.

11.5.4.3 *Pesticides*

In a Consensus Statement[498] prepared by scientists who met during 2007 to consider the environmental links to PD, risk factors were categorized using the Institute of Medicine categories for strength of evidence. For pesticides as a group, they concluded that "limited but suggestive evidence of an association" exists for greater PD risk among farmers and agricultural workers and for people occupationally exposed to pesticides, without being able to specify individual chemicals. Others have reached similar conclusions.[499,500,501,502] Once pesticides are specified, the Consensus Statement concluded that "inadequate/insufficient evidence exists to determine whether an association exists." Specific pesticides included the now-banned OC pesticide dieldrin, as well as three others: paraquat, rotenone and maneb. These latter three demonstrate, in animal studies, toxicity to nigral dopaminergic neurons, i.e., biologic mechanisms that are plausibly linked to PD risk.

Ongoing research has continued to confirm the general association of PD with occupational pesticide use while adding to evidence of possible associations for specific pesticides. For example, this work has included finding associations between PD and OC insecticides[503] (including dieldrin[504]) as well as associations with two others, (2,4-D and pyrethrins), that also demonstrate effects on dopaminergic neurons in animal studies.[505] Overall however, the evidence of links to specific pesticides remains limited. A review of the toxicological literature notes multiple reasons including, for example, the likely involvement of multiple molecular targets that can promote neurodegeneration and thus a need to evaluate mixtures of compounds potentially working in concert to damage neurons via actions at different sites.[506]

11.5.4.4 *PCBs and other POPs, Solvents, Additional Metals*

Finally, there is some emerging evidence of associations between several other environmental exposures and PD.[507] For example, epidemiological data indicate an association between PD and women's occupational exposure to PCBs, with animal data from studies of primates and rodents indicating that PCBs can reduce dopamine levels in the substantia nigra.

In addition, PD may be associated with occupational exposure to several organic solvents and, like PCBs, damage is seen in the substantia nigra as well as other parts of the brain. Metals other than lead, including manganese,[508] iron and copper may also be implicated in PD. This evidence comes from occupational exposure in adults and mechanisms at play include oxidative stress and protein aggregation, important risk factors in PD. Within the Consensus Statement described above, these exposures also fell within the IOM category of "inadequate/insufficient evidence to determine whether an association exists."

11.5.5 *Early Life Exposures and Parkinson's Disease*

Again, as noted for AD, insofar as a continuum may exist whereby PD shares common risk factors with obesity or other conditions that include excess inflammation or oxidative stress, or

498 Bronstein J et al (2009) Meeting Report: Consensus Statement – Parkinson's Disease and the Environment: Collaborative on Health and the Environment and Parkinson's Action Network (CHE PAN) Conference 26-28 June 2007. *Environmental Health Perspectives*; 117:117-121.
499 Brown RC et al (2005) Neurodegenerative Diseases: An Overview of Environmental Risk Factors. *Environmental Health Perspectives*; 113:1250-1256.
500 Brown TP et al (2006) Pesticides and Parkinson's Disease – Is There a Link? *Environmental Health Perspectives*; 114:156-164.
501 Ascherio A et al (2006) Pesticide Exposure and Risk for Parkinson's Disease. *Annals of Neurology*; 60:197-203.
502 Frigerio R et al (2006) Chemical Exposures and Parkinson's Disease: A Population-Based Case–Control Study. *Movement Disorders*; 21(10):1688–1692.
503 Elbaz A et al (2009) Professional Pesticide Exposure to Pesticides and Parkinson Disease. *Annals of Neurology*; 66:494-505.
504 Weisskopf MG et al (2010) Persistent organochlorine pesticides in serum and risk of Parkinson disease. *Neurology*; 74(13):1055-1061.
505 Tanner CM et al (2009) Occupation and Risk of Parkinsonism – A Multicenter Case-Control Study. *Archives of Neurology*; 66(9):1106-1113.
506 Hatcher JM et al (2008) Parkinson's disease and pesticides: a toxicological perspective. *Trends in Pharmacological Sciences*; 29(6):322-329.
507 As reviewed in Stein J et al (2008) *op. cit.* Chapter 8: Environmental Factors in the Development of Parkinson's Disease.
508 Criswell SR et al (2011) Reduced uptake of [^{18}F]FDOPA PET in asymptomatic welders with occupational manganese exposure. *Neurology*; 76:1296–1301.

indeed early life exposures suspected as obesogenic, it is conceivable that known or suspected environmental risks are also shared.

11.5.5.1 *Recap of Endocrine Disrupting Substances Suspected as Obesogens*

Should a stronger relationship between obesity and PD be confirmed, it is reasonable to consider suspected obesogens as co-morbid risk factors for PD. Summarizing from Section 10.3.2.3 above, these exposures would include drug DES, BPA, phthalates, organotins, PBDEs, polyfluoroalkyl chemicals, OC pesticides, and PCBs.

It is important to emphasize that direct links between these exposures and PD is not meant or implied by this summary. Rather, each should be considered in light of the strength of evidence discussed in these earlier sections and the potential for a continuum of inter-related risk factors for multiple conditions and diseases, including PD.

11.5.5.2 *Air Pollution*

In the air pollution studies noted above and described in more detail in Section 11.4.6.2 with respect to AD, results point to sub-clinical pathology beginning in childhood and among young adults. Healthy children had multiple markers of respiratory and systemic inflammation, including inflammation capable of reaching the brain, systemic circulation of particulate matter, immunodysregulation, and neuroinflammation/neurodegeneration, the latter indicated by multiple markers in the brain of neuroinflammation and oxidative stress, leading the team to conclude that long term exposure to high levels of air pollution should be considered a risk factor for both AD and PD.[509]

11.5.5.3 *Pesticides*

A literature review[510] of evidence for neurodevelopmental origins of PD describes "compelling evidence from animal models" for perinatal pesticide exposure causing a reduction in the number of dopamine neurons or causing increased susceptibility to degeneration of these neurons with subsequent environmental exposures or via aging alone. These authors consider this evidence potentially relevant in linking PD with the DOHaD model.

For example, they note that for the two pesticides maneb and paraquat, studies in adult mice indicate that combined exposure causes synergistic decreases in motor activity and dopamine and increased damage to dopaminergic neurons in the brain. On the basis of these findings, investigators exposed animals to these chemicals singly and in combination during early development. Combined exposure to both pesticides perinatally resulted in loss of dopamine and reduced dopamine neurons in the substantia nigra with effects greater than those seen in adults. As well, combined exposures in infancy enhanced vulnerability to the same chemicals when exposed as adults. Additional experiments showed that fetal exposure to maneb increased vulnerability to paraquat in adulthood, measured again as reduced levels of both dopamine and dopaminergic neurons. Effects were more pronounced in male mice, correlating to the known higher prevalence of PD in human males. These results illustrate the "multiple hit" concept described in Section 11.3.1 above.

This review also describes animal studies of perinatal exposure to OC pesticides and resulting persistent alterations in the nigrostriatal system in the brains of male progeny lasting into adulthood. Additional experiments exposing mice to the OC pesticide dieldrin prenatally and via lactation resulted in no immediate outcomes but at 12 weeks investigators found biomarkers of adverse effects in the dopaminergic system and further noted that dieldrin levels at 12 weeks were below the limit of detection suggesting changes in gene expression persisting into adulthood when the toxic agent is no longer present.

509 See multiple citations in Section 11.4.6.2 above.

510 Barlow BK et al (2007) The gestational environment and Parkinson's disease: Evidence for neurodevelopmental origins of a neurodegenerative disorder. *Reproductive Toxicology*; 23:457-470.

11.6 Developmental Neurotoxicity – Summary of Environmental Risk Factors

Finally, it is important to at least summarize the compelling evidence[511,512,513,514] that exists of the potential for permanent harm to the developing brain from exposure to a few well-studied substances such as lead,[515] mercury,[516] arsenic,[517] manganese,[518] alcohol[519] and certain organic solvents,[520,521] certain pesticides,[522,523] PAHs,[524 525] ETS,[526] and PCBs.[527] As well, evidence exists for associations with developmental neurotoxicity and a wider range of substances, (including as chemical mixtures[528]), including phthalates,[529] BPA,[530] dibutyltin,[531] PBDEs,[532,533,534] and other POPs,[535,536,537] triclosan,[538] and artificial food colours and additives.[539] Concern about the potential for developmental neurotoxicity also exists for dozens of substances that are known to be toxic to the adult brain and hundreds more that are known to be neurotoxic in (adult) animal models.[540]

A comparison of the above list of substances indicates considerable overlap between exposures suspected in developmental neurotoxicity and those where evidence indicates associations with AD, PD or various conditions and diseases that may be co-morbid risk factors such as obesity, metabolic syndrome, diabetese and CVD.

11.7 Brain Impacts, Focus on Alzheimer's and Parkinson's Disease – Key Points

- Alzheimer's Disease (AD), and related dementias such as vascular dementia, as well as Parkinson's Disease (PD) are considered part of a rapidly growing epidemic related to an

511 Julvez J and Grandjean P (2009) Neurodevelopmental Toxicity Risks Due to Occupational Exposure to Industrial Chemicals during Pregnancy. *Industrial Health*; 47: 459–468.
512 Gilbert SG et al (2010) Scientific and policy statements on environmental agents associated with neurodevelopmental disorders. *Journal of Intellectual and Developmental Disability*; 35(2):121–128.
513 McElgunn B (2010) The Developing Brain: A largely overlooked health endpoint in risk assessments for synthetic chemical substances. *International Journal of Disability, Development and Education*; 57(3):315-330.
514 Kalia M (2008) Brain development: anatomy, connectivity, adaptive plasticity, and toxicity. *Metabolism Clinical and Experimental*: 57(Suppl 2):S2–S5.
515 Lanphear BP et al (2005) Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environmental Health Perspectives*; 113:894–9.
516 Oken E and Bellinger DC (2008) Fish consumption, methylmercury and child neurodevelopment. *Current Opinion in Pediatrics*; 20:178–183.
517 Wasserman GA et al (2004) Water arsenic exposure and children's intellectual function in Araihazar, Bangladesh. *Environmental Health Perspectives*; 112:1329–1333.
518 Takser L et al (2003) Manganese, monoamine metabolite levels at birth, and child psychomotor development. *Neurotoxicology*; 24:667–674.
519 Sokol RJ et al (2003) Fetal Alcohol Spectrum Disorder. *Journal of the American Medical Association*; 290(22):2996-2999.
520 White RF and Proctor SP (1997) Solvents and neurotoxicity. *Lancet*; 349(9060):1239-43.
521 Till C et al (2005) Vision abnormalities in young children exposed prenatally to organic solvents. *Neurotoxicology*; 26(4):599-613.
522 Colborn T (2006) A Case for Revisiting the Safety of Pesticides: A Closer Look at Neurodevelopment; *Environmental Health Perspectives*; 114:10–17.
523 Eskenazi B et al (2008) Pesticide Toxicity and the Developing Brain. *Basic & Clinical Pharmacology & Toxicology*; 102:228–236.
524 Perera FP et al (2006) Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environmental Health Perspectives*; 114:1287–92.
525 Perera FP et al (2009) Prenatal Airborne Polycyclic Aromatic Hydrocarbon Exposure and Child IQ at Age 5 Years. *Pediatrics*; 124:e195–e202.
526 Herrmann M et al (2008) Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. *Current Opinion in Pediatrics*; 20:184–190.
527 Eubig PA et al (2010) Lead and PCBs as Risk Factors for Attention Deficit/Hyperactivity Disorder. *Environmental Health Perspectives*; 118:1654–1667.
528 Crofton KM (2007) Thyroid disrupting chemicals: mechanisms and mixtures. *International Journal of Andrology*; 31:209-223.
529 Engel SM et al (2010) Prenatal Phthalate Exposure Is Associated with Childhood Behavior and Executive Functioning. *Environmental Health Perspectives*; 118:565–571.
530 Braun JM et al (2009) Prenatal Bisphenol A Exposure and Early Childhood Behavior. *Environmental Health Perspectives*; 117:1945–1952.
531 Jenkins SM et al (2004) Structure-activity comparison or organotine speicies: Dibutyltin is a developmental neurotoxicant *in vitro* and *in vivo*. *Developmental Brain Research*; 151:1-12.
532 Schreiber T et al (2010) Polybrominated Diphenyl Ethers Induce Developmental Neurotoxicity in a Human *in vitro* Model: Evidence for Endocrine Disruption. *Environmental Health Perspectives*; 118:572–578.
533 Chevrier J et al (2010) Polybrominated Diphenyl Ether (PBDE) Flame Retardants and Thyroid Hormone during Pregnancy. *Environmental Health Perspectives*; 118:1444–1449.
534 Herbstman JB et al (2010) Prenatal Exposure to PBDEs and Neurodevelopment. *Environmental Health Perspectives*; 118:712–719.
535 Roze E et al (2009) Prenatal Exposure to Organohalogens, Including Brominated Flame Retardants, Influences Motor, Cognitive, and Behavioral Performance at School Age. *Environmental Health Perspectives*; 117:1953–1958.
536 Korrick SA and Sagiv SK (2008) Polychlorinated biphenyls, organochlorine pesticides and Neurodevelopment. *Current Opinion in Pediatrics*; 20:198–204.
537 Kodavanti PRS and Curras-Collazo MC (2010) Neuroendocrine actions of organohalogens: Thyroid hormones, arginine vasopressin, and neuroplasticity. *Frontiers in Neuroendocrinology*; 31:479-496.
538 Paul KB et al (2009) Short-term Exposure to Triclosan Decreases Thyroxine *In vivo* via Upregulation of Hepatic Catabolism in Young Long-Evans Rats. *Toxicological Sciences*; 113(2):367–379.
539 McCann D et al (2007) Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: A randomised, double-blinded, placebo-controlled trial. *Lancet*; 370:1560–1567.
540 Grandjean P and Landrigan Pj (2006) Developmental neurotoxicity of industrial chemicals. *Lancet*; 368(9553): 2167-2178.

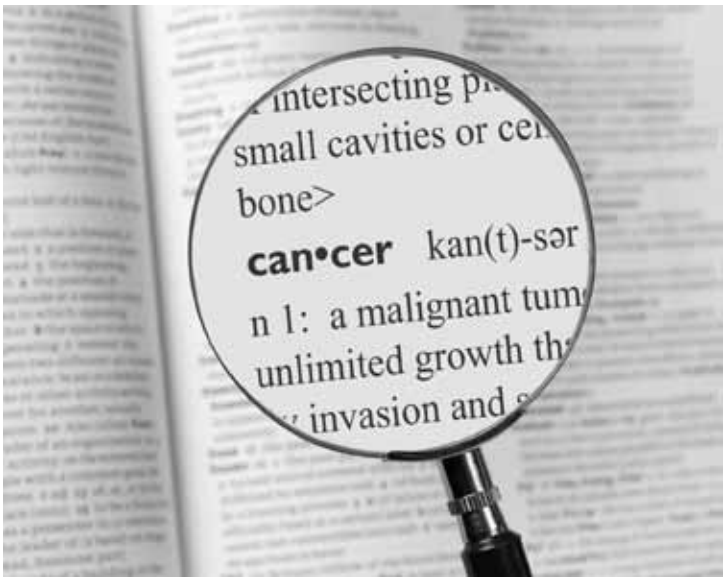
aging population and the convergence of multiple risk factors.

- About 500,000 Canadians have dementia (about 63% is AD) and this number is predicted to be 1.1 million in 2038. PD affects more than 100,000 people, a number predicted to double by 2050.
- Advancing age is a key risk factor. The small proportion of AD associated with genetic risk factors typically manifests at an earlier age than other dementias of old age. Gender is a risk factor for AD in post-menopausal women.
- Strictly genetic risk factors account for about 5-10% of PD with the balance caused by complex gene-environment interactions that are not fully understood. Gender is a risk factor for PD with men having twice the risk as women.
- Research indicates that healthy brain aging results from a lifelong process beginning with healthy brain development and creation of "brain reserve." Research into both AD and PD indicates that the timing and/or likelihood of their occurrence in old age results from a complex combination of lifelong influences ("multiple hits" and the "silent toxicity" or latency of some risk factors), including epigenetic influences in the womb, that contribute to "brain reserve."
- A continuum of common risk factors exists for obesity, metabolic syndrome, diabetes, CVD, AD and vascular dementia. Obesity may also be a risk factor for PD though this evidence is limited and inconsistent.
- Common risk factors include the same nine biomedical and behavioural risk factors noted for CVD as well as the additional risk factors noted for obesity and diabetes.
- Of particular importance among the common risk factors are those where circumstances contribute to inflammation and oxidative stress and thence to disrupted insulin signaling with some researchers calling AD "diabetes of the brain." Links to PD pathologies are more specific to effects of oxidative stress in the brain.
- For environmental exposures in adults, insofar as a continuum is apparent whereby AD, and to a more limited extent PD, share common risk factors with other chronic diseases, the environmental exposures associated with these other conditions are also relevant. Recapping from the discussions about CVD and diabetes, these exposures include: air pollution, lead, BPA, phthalates,OP pesticides, and POPs.
- Some adult exposures are more directly implicated in AD including lead exposure (perhaps due to lifetime chronic exposure) and air pollution (also implicated in PD). Although there is less evidence, associations have been suggested with pesticides (PD via occupational exposure), PCBs and other POPs (AD, dementia/cognitive decline and PD), solvents (PD), and some additional metals (manganese, iron and copper with possible links to PD).
- Likewise for early life exposures, the apparent continuum of several chronic conditions and diseases, including shared risk factors, is also relevant for AD and to some extent PD. However, for early exposures, the DOHaD concept and epigenetic mechanisms are involved as well as related issues of "brain reserve," the "multiple hit" concept and "silent toxicity"/latency.
- Recapping early life exposures of concern in terms of being risk factors common to an apparent continuum of multiple chronic diseases, including AD, these exposures include: air pollution, organic solvents, chlorophenoxy herbicides, trihalomethanes, ionizing radiation, lead, ETS, mercury, OC and OP pesticides, nitrates in drinking water, arsenic, phthalates, brominated flame retardants, polyfluorinated compounds, BPA, phthalates, organotins, and PCBs.
- Early life exposures for which there is more direct evidence of possible associations with later life neurodegeneration include air pollution (associations with AD, and to lesser extent PD) and lead (associations with AD).
- Comparing the list of substances suspected in developmental neurotoxicity indicates considerable overlap with substance where evidence indicates associations with AD, PD

or various conditions and diseases that may be co-morbid risk factors such as obesity, metabolic syndrome, diabetese and CVD.

12.0 Cancer

12.1 Prevalence



In recent years, cancer has overtaken CVD as the leading cause of death in Canada. In the annual reports on cancer statistics, for 2009,[541] 2010,[542] and 2011,[543] the Canadian Cancer Society (CCS) reports on various cancer statistics to the end of 2004, 2005 and 2006, 2006 and 2007, respectively, as well as providing estimates for cancer incidence during each of 2009, 2010 and 2011. In addition to the overview of cancer statistics noted in Table 2 (in Section 2 above), the CCS states that nearly half of all people in Canada (40% of women and 45% of men) are expected to develop cancer in their lifetime and while mortality from cancer is generally declining, approximately one out of every four Canadians will die from cancer. The CCS further reports that:

- Since the 1980s, age-standardized data show that the cancer incidence rate has fluctuated but remained relatively stable in Canada for men and increased slightly in women although the overall number of cases in both sexes has steadily increased due to a growing and aging population. As well, the gap in incidence rates between women and men is narrowing.
- Three types of cancer account for the majority of new cases in each sex: prostate, lung and colorectal in males and breast, lung and colorectal in females. Therein, for both sexes, cancers of the breast, prostate, colorectal and lung (diagnosed between 1997 and 2006), are the most prevalent, together accounting for nearly 60% of 10-year prevalent cases.
- Overall, the most common cancers, by a considerable margin, are breast cancer (40% of 10-year prevalent cancer cases in women) and prostate cancer (38% of 10-year prevalent cancer cases in men).
- Lung cancer remains the leading cause of cancer death (over 27% of all cancer deaths) for both men and women and colorectal cancer is the second leading cause (12% of all cancer deaths).
- While cancer is mainly a disease of older age (43% of new cases and 61% of deaths were predicted for 2010 to occur among those over 70 years old), 30% of new cases and 17% of cancer deaths in 2009 were predicted to occur among young and middle-aged adults (20 to 59 years).
- Mortality rate is declining for males in most age groups and for females under 70 years of age.
- Between 1998 and 2007, thyroid cancer incidence rates rose an average of 7% per year for males and 9% per year for females while liver cancer rose by an average of 4% per year for males and just over 2% per year for females.
- Childhood cancer remains very rare though it continues to be the leading cause of illness-related death among children in Canada.
- Finally, with a particular focus on cancer in adolescents and young adults (aged 15 to

541 Canadian Cancer Society (2009) *Canadian Cancer Statistics 2009*. Toronto, ON: Canadian Cancer Society.
542 Canadian Cancer Society (2010) *Canadian Cancer Statistics 2010*. Toronto, ON: Canadian Cancer Society.
543 Canadian Cancer Society's Steering Committee (2011) *Canadian Cancer Statistics – 2011*. Toronto, ON: Canadian Cancer Society.

29) the 2009 CCS report on cancer statistics in Canada notes that for the ten year period between 1994 and 2005, there was a significant increase in cancer rates overall in this age group including statistically significant increases in testicular cancer and soft tissue sarcoma (the latter increasing only since 2001) in young men and thyroid cancer in young women.

- Within this focus on adolescents and young adults, the report notes that in this age range a transition is apparent in the types of cancer from those cancers common during childhood to those diagnosed in adults.
- While overall cancer rates are stabilizing and mortality rates are dropping, cancer incidence is rising among young women aged 20 to 39 and certain cancers, particularly thyroid cancer, account for much of this increase.
- In addition, testicular cancer has increased in adolescent and young adult men aged 15 to 30 since 1996 while soft tissue sarcoma incidence has increased only since 2001. The increase in testicular cancer is particularly significant with a 2.7% increase per year with no well-understood risk factors to explain it. Data from European countries[544] note similar increases and a current lifetime risk for testicular cancer approaching 1%. Indeed, this rising trend in recent decades is seen worldwide in industrialized countries.[545]
- A 2006 analysis[546] of the statistics for young adults (aged 20 to 44) notes similar increases between 1983 and 2005, particularly for thyroid cancer and non-Hodgkin lymphoma in young women and testicular cancer in young men.

These are highlights of major trends across the population including noting those cancers that can affect large numbers of people and/or that have been significantly increasing in the past 10 to 15 years. These cancers include breast (women), prostate (men), lung and colorectal (both sexes), thyroid (both sexes but higher in women, especially young women), and testicular and liver cancers (men) and soft tissue sarcoma (young men).

Many additional cancers occur across the population, and are not highlighted in the above summary. Noteworthy among these is bladder cancer in men because it is the next most common cancer after the top three already noted and is associated with a range of different chemical exposures (as noted further in Sections 12.4 and 12.6 below).

For children, cancer types are generally different than among adults with the most common being leukemia, cancers of the brain and nervous system and lymphoma. Cancer in children is very rare and data for Canada show no significant rise in cancer incidence since the mid-1980s. During the same time in the much larger populations in both the U.S.[547] and the European Union,[548] the incidence of the same types of cancers that occur in Canadian children rose steadily, by about 1% per year between 1970 and 1999 with rates rising faster before 1990 but continuing to increase slowly since then. The fact that Canadian data do not indicate an increase may be due to rare events in a small population not showing up as statistically significant increases over time.

While there is some debate as to whether the increases seen in childhood cancers in the larger U.S. and EU populations reflect improved diagnosis or real increases, no debate exists over the fact that certain cancers are significantly increasing in adolescents and young adults. Whether looking at the increases seen in the age 15 to 29 years group (as reported in the 2009 CCS report described above) or seen in young adults aged 20 to 44 (as noted in the above-cited 2006 Cancer Care Ontario report), cancer incidence in young adults in Canada increased by more than 2% per year since the 1970s until the present.

544 Bray F et al (2006) Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. *International Journal of Cancer;* 29:54-61.

545 Huyghe E et al (2003) Increasing incidence of testicular cancer worldwide – a review. *Journal of Urology*; 170:5-11.

546 Cancer Care Ontario (2006) *Cancer in Young Adults in Canada*.

547 Altekruse SF et al (eds) (2010) SEER Cancer Statistics Review, 1975-2007, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site, 2010.

548 Steliarova-Foucher E et al (2004) Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *The Lancet* 364: 2097-2105.

12.2 Interacting Risk Factors

Cancer is not one disease but many, depending on the type of cancer and location in the body. Three broad categories of risk factors for cancer include: genetic inheritance, lifestyle and environment. However, much complexity exists within each of these three areas including multiple interactions within and between each overall category. Given that all cancers result from generally long-term, multi-stage processes, all of which can be influenced by multiple and interacting variables, the notion of apportioning risk, (also referred to as attributable fractions), into separate categories, such as genetics, diet, smoking, occupation, environment, etc., is increasingly criticized as overly simplistic.[549,550]

For example, in its 2008-09 Annual Report the President's Cancer Panel in the U.S.,[551] notes that the widely quoted estimate of the "attributable fraction" of cancer due to pollution of two percent as determined by Doll and Peto[552] in the early 1980s is "woefully out of date." Their calculations for the attributable fraction from occupation, industrial products, and medicines and medical procedures were also very small and have since been similarly disputed for multiple reasons. For example, shortcomings in their calculations, as noted by the President's Cancer Panel report, include an overly narrow focus on epidemiological data from workers in large industries to the exclusion of: minorities; deaths among those older than age 65; exposures in smaller workplaces; and indirect contact with carcinogens such as can occur among family members via take-home exposures. Nor did they account for crucial issues such as the interaction or synergism of environmental variables, the greater vulnerability of key life stages (prenatal, early life and puberty), or the complexity of multiple aspects of gene-environment interactions. [553]

Where genetic inheritance can be specifically identified as causing cancer, that is, where a single-gene inherited cancer has been identified, these are considered to account for less than 5% of the overall cancer burden in humans.[554] An additional influence of genetic inheritance that is known to impact susceptibility to cancer arises from genetic polymorphisms – that is, alternate forms of genes in a population. Genetic polymorphisms, or gene variants, can help to explain why differential effects of environmental exposures occur in a population. An example is noted in Section 13.2.2 below with respect to genetic differences and risk factors for asthma susceptibility. These genetic variations determine many aspects of form and function in the body such as differences in eye or skin colour, or the ability to break down toxic substances in the body. For example, it is well recognized that blonde hair and light skin increase susceptibility to sunburn and later skin cancer. In an example concerning pesticide exposure, a study of children in Quebec found a greater risk of leukemia among children carrying certain genetic polymorphisms and who were exposed to pesticides in the womb.[555,556] The polymorphisms affected the presence of liver enzymes that metabolize foreign substances in the body, including pesticides. While the role of these enzymes in pesticide metabolism or the reason the specific polymorphisms were linked to cancer susceptibility is not fully understood, this study demonstrates a complex interplay between genetic and environmental factors in cancer susceptibility.

Other endogenous (internal to the body) processes that are cancer risk factors include cellular detoxification processes that can produce oxygen radicals that damage DNA (and thus lead to cancer). However, these processes are not wholly internal as they will be influenced by such variables as diet or stress, both of which will be influenced by socio-economic status and other

549 Steingraber, S (2010) *Living Downstream: An Ecologist's Personal Investigation of Cancer and the Environment*, DaCapo Press, 2ND Edition.

550 Clapp RW (2007) *Environmental and Occupational Causes of Cancer, New Evidence, 2005-2007*. Lowell Center for Sustainable Production, University of Massachusetts, Lowell.

551 Reuben S for the President's Cancer Panel (2010) *Reducing Environmental Cancer Risk – What We Can Do Now*. 2008-2009 Annual Report, President's Cancer Panel. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

552 Doll R and Peto R (1981) The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *Journal of the National Cancer Institute*; 66:1191-308.

553 See also: White M (2008) The Causes of Cancer: What Has Happened Since Doll and Peto's Landmark Paper? *Epidemiology*; 19(1):S226. Abstracts: ISEE 19th Annual Conference, Mexico City, Mexico, September 5-9, 2007.

554 Sonnenschein C and Soto AM (2008) Theories of carcinogenesis: An emerging perspective. Review in *Seminars in Cancer Biology;* 18:372-77.

555 Infante-Rivard C et al (1999) Risk of childhood leukemia associated with exposure to pesticides and with gene polymorphisms. *Epidemiology;* 10:481-487.

556 Infante-Rivard C and Sinnett D (1999) Preconceptional paternal exposure to pesticides and increased risk of childhood leukaemia. *Lancet*; 354:1819.

SDOH as discussed throughout this report. Another example of endogenous processes leading to cancer underscores the fact cancer is predominantly a disease of the elderly. A key reason for this later-life susceptibility is because aging cells are more likely to make more errors in DNA replication than younger cells. The longer an individual lives, the more DNA copying errors become possible given the billions of cell divisions that continue throughout the lifetime.

The broad area of exogenous (external to the body) factors that can contribute to cancer includes the behavioural risk factors described in Section 4.2, the so-called "big three" including tobacco, diet and exercise, as well as exposure to biological and physical agents and chemicals, including some viruses, radiation and multiple chemicals (as discussed further below). Excess alcohol consumption, stress and obesity[557] are also known cancer risk factors. However, as also discussed in Section 4.2, the SDOH strongly influence these behavioural risk factors, as they also influence the likelihood of obesity and excess stress. Interactions with environmental contaminants further complicate this picture.

The "big three" behavioural risk factors (tobacco, diet and exercise), and the underlying SDOH are clearly understood as making a major contribution to the incidence of cancer. Notably, while incidence and mortality for most cancers is higher among those of low socio-economic status, this situation is inverted for breast cancer in Canada with women of higher socio-economic status having higher rates of breast cancer.[558]

It is unknown and likely unknowable what percentage of cancers are initiated or promoted specifically by environmental factors such as radiation and chemical exposures (including where these are occupational exposures). Nor is it particularly useful to seek an answer to this question given the reality of complex interactions. What is increasingly apparent is a very large and growing body of evidence pointing to multiple environmental and/or occupational exposures as contributors to many different cancers, including the two most prevalent cancers in the population – cancers of the breast and prostate – as well as other common cancers. Included in this evidence is the growing understanding of the special vulnerability of early life stages *in utero* and during childhood and adolescence.

12.3 Evolving Theories of Carcinogenesis

Although scientists have come to understand a great deal about cancer, there is much still to learn and theories of carcinogenesis continue to evolve. These new ideas are briefly explored here because knowledge about carcinogenesis is increasingly influenced by advances in the field of epigenetics, particularly investigations into why and how developmental windows of vulnerability can set in motion processes that can create a greater likelihood of cancer later in life.

Beyond the approximately 5% of cancers for which a direct genetic or hereditary cause is identified and understood, there are important recent advances in theories on cancer causation, arising from chemical, physical or biological agents in the environment. The oldest and largest body of evidence describes what is referred to as the somatic mutation theory. It posits that carcinogens have a mutagenic mode of action, that is, they cause a mutation in cellular DNA which then causes normal cells to become malignant, new cancerous cells to proliferate, and ultimately spread to other parts of the body.[559] The genetic mutations occur on the genes that regulate cell division, cell survival and/or DNA repair processes. These genes are referred to as tumour suppressor genes and cell proliferation regulator genes, also known as protooncogenes, which, when mutated, turn into cancer-causing genes. Examples of mutagenic carcinogens include radiation and vinyl chloride.

To the above admittedly overly simplified summary of cancer genetics can be added layers of complexity that arise from the expanding knowledge about epigenetic mechanisms, which, as introduced in Section 8.2 above, can change gene expression under the influence of external factors, such as environmental contaminants, without also changing the underlying genetic

557 Renehan AG et al (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*; 371(9612):569-78.

558 Borugian MJ et al (2011) Breast cancer incidence and neighbourhood income. *Health Reports*; 22(2):1-7. Statistics Canada Catalogue no. 82-003-X.

559 Weinberg, RA (1998) *One Renegade Cell: How Cancer Begins*. Basic Books; New York.

sequence in DNA. This knowledge arises particularly from investigations of endocrine disrupting substances, since one key mechanism of endocrine disruption is altered gene expression.[560]

The field of epigenetics has dramatically expanded the depth and complexity of theories on carcinogenesis. Epigenetic mechanisms and events are increasingly seen as central to the understanding of how most cancers develop and progress.[561] They play key roles across virtually every step of tumour development and progression.[562] Epigenetic mechanisms are also involved in modifying the activity of genes that regulate the development of reproductive organs, such as the breast and prostate that then exhibit greater cancer susceptibility later in life.[563]

In a review[564] of research findings about epigenetics and environmental chemicals, the authors note that epigenetic alterations are apparent in experimental and epidemiological studies of numerous compounds that are either known or suspected carcinogens including the metals cadmium, nickel, chromium and arsenic, the drug DES, pesticides such as vinclozolin and methoxychlor, BPA, benzene and particulate air pollution, and POPs, particularly dioxin. While this summary of these findings is a necessary oversimplification and much variation exists in the kinds of epigenetic alterations seen across these many substances, a common result in the experimental evidence is that these compounds cause biochemical changes in a healthy animal or person that correspond to circumstances that are more profoundly apparent when cancer is present (specifically, alterations in DNA methylation).[565] It is also the case for the metal lead, and likely other contaminants, that multiple modes of action are apparent that may contribute to carcinogenesis, including epigenetic mechanisms.[566]

As in other areas of epigenetic research, in the investigation of cancer, epigenetics is increasingly providing explanations of the subcellular activity that arises within and around the genetic information coded in cellular DNA. This field sheds light on the biochemical mechanisms of how cellular genetic information interacts with the other building blocks of cells and tissues during normal development and the maintenance of homeostasis and, for the sake of this discussion, the impact of exposure to carcinogens. By helping to explain how chemicals interfere with these biochemical processes epigenetics may also allow for the detailed understanding available from a small number of substances to assist with understanding the toxic effects of so many others about which less is known.

However, it is worth noting that, despite the formidable advances in genetics and epigenetics in expanding the understanding of carcinogenesis, some researchers point to central limitations. They state that cancer is neither a genetic nor a cellular problem but rather a tissue organization problem.[567] Across existing theories of carcinogenesis, including advances in epigenetics, they note an inherently reductionist scientific paradigm dominated by genetic determinism that cannot explain a growing body of findings in cancer research.[568]

To note just two examples, experiments have shown that cancer arose in carcinogen-exposed rat mammary gland stroma, (i.e., the support tissue in the breast vs. the mammary epithelial cells), when it was combined with unexposed, normal mammary epithelial cells. But, the reverse did not occur, that is, combining carcinogen-exposed mammary epithelial cells with unexposed stroma cells did not result in cancer.[569] Similar results are observed in other studies such as when cells from early embryos are placed in ectopic locations, (i.e., where they don't belong), in an adult animal they result in tumours called teratocarcinomas. But when the teratocarcinoma cells

560 Edwards TM and Myers P (2007) Environmental Exposures and Gene Regulation in Disease Etiology. Review. *Environmental Health Perspectives;* 115(9):1264-1270.
561 Jones PA and Baylin SB (2002) The fundamental role of epigenetic events in cancer. *Nature Reviews; Genetics;* 3: 415–428.
562 Herceg Z (2007) Epigenetics and cancer: toward an evaluation of the impact of environmental and dietary factors. *Mutagenesis;* 23(2):91-103.
563 Edwards TM and Myers P (2007) Environmental Exposures and Gene Regulation in Disease Etiology. Review. *Environmental Health Perspectives*; 115(9):1264-1270.
564 Baccarelli A and Bollati V (2009) Epigenetics and environmental chemicals. *Current Opinions in Pediatrics*; 21:243-251.
565 Feinberg AP et al (2006) The epigenetic progenitor origin of human cancer. *Nature Reviews Genetics*; 7:21-33.
566 Silbergeld EK et al (2000) Lead as a Carcinogen: Experimental Evidence and Mechanisms of Action. *American Journal of Industrial Medicine;* 38:316-323.
567 Soto AM and Sonneschein C (2006) Emergentism by default: A view from the bench. *Synthese*; 151:361-376.
568 Sonnenschein C and Soto AM (2008) Theories of carcinogenesis: An emerging perspective. Review. *Seminars in Cancer Biology*; 18:372-377.
569 Maffini MV et al (2006) The stroma as a crucial target in rat mammary gland carcinogenesis. *Journal of Cell Science;* 1495-1502.

were injected into early embryos, normal tissues and organs developed. Hence, embryonal cells produced tumours when misplaced in adult tissues but the same cancer cells reverted to normalcy when placed in an early stage embryo.[570]

These and many other results lead to a conclusion of reciprocity of signals between cells and tissues that make cause and effect relationships difficult to establish within the traditional theory of carcinogenesis arising from the somatic mutation of cellular DNA. These researchers propose instead a theory of cancer as a developmental process, akin to organogenesis but gone awry, happening at the tissue (as opposed to the cellular) level of biological complexity. While the details are beyond the scope of this review, this theory is noted here because it captures the views of leading scientists in this field who seek a more holistic framework to explain observed cancer phenomena. Viewed from their "tissue organization field theory" they can more logically account for reciprocal interactions and circular causation observable in multiple studies of cancer and indeed other biological phenomena.

As theories of carcinogenesis continue to evolve, central conclusions from the current state of knowledge about cancer are that epigenetic mechanisms are involved throughout and that they are centrally involved in early life events that can lead to later life cancer. Further, when viewed from a tissue level of organization, the action of carcinogens on and within individual cells can be observed in numerous studies as less relevant as carcinogen-induced changes in cell-to-cell or tissue-to-tissue interaction.[571] This latter conclusion echoes the multi-variant and interacting complexity of the MDOH and also points provocatively and hopefully to cancer as susceptible to being normalized, that is, reversible.

Finally, the theory that cancer is caused by the genotoxic and mutagenic action of chemicals is the only mode of action that is recognized in regulatory assessments of carcinogens, a fact that is directly challenged by epigenetic cancer research and which thus has significant policy implications.

12.3.1 Biomarkers and Epimutagens

These many advances in the biochemistry of carcinogenesis may provide opportunities for earlier detection of cancer or its epigenetic precursors through the use of biomarkers (measurable molecular changes) that can indicate the occurrence of cancer, pre-cancerous conditions, or epigenetic activity associated with the subsequent development of cancer. Such biomarkers may be of broad public health significance in terms of offering improved means of either halting or preventing cancer development. Fundamental policy issues also arise when such biomarkers point to early life, (including prenatal) exposures being linked to later life cancer.

For example, in a review[572] of studies of pregnant mothers exposed to known genotoxic carcinogens, particularly cigarette smoke, a molecular epidemiology approach is described. This approach uses the fact that, for most genotoxic cancers, an exposure-disease continuum can be discerned where molecular changes (biomarkers), can indicate either known risks or specific stages towards the development of cancer. Biomarkers can include, for example, cord blood levels of known carcinogens such as some metals or cotinine (a marker of tobacco smoke). Biomarkers can also include DNA and protein adducts which are metabolites of an originally genotoxic compound such as PAHs. Once metabolized, these compounds can bind to DNA or proteins (as adducts), a step that is considered to initiate carcinogenesis.

Biomarkers of early effects of genotoxic agents are also measurable, such as mutation frequency in specific genes that may not be involved in carcinogenesis but that are understood to reflect mutations in genes involved in cell-cycle control. The above-cited study found, in a review of other studies and in their own investigations, that measurements of the frequencies of three

570 Stewart TA and Mintz B (1981) Successful generations of mice produced from an established culture line of euploid teratocarcinoma cells. *Proceedings of the National Academy of Sciences, U.S.A*, 78:6314-6318, as reviewed in Soto and Sonnenschein (2006), *op cit*.

571 Sonnenschein C and Soto AM (2000) The somatic mutation theory of carcinogenesis: why it should be dropped and replaced. *Molecular Carcinogenesis*; 29:1-7.

572 Godschalk RWL and Kleinjans JCS (2008) Characterization of the Exposure-Disease Continuum in Neonates of Mothers Exposed to Carcinogens during Pregnancy. *Basic and Clinical Pharmacology and Toxicology;* 102:109-117.

types of biomarkers were increased in the cord blood of neonates whose mothers were exposed to carcinogens during pregnancy and higher levels correlated with proxies of health effects such as reduced birth weight. Notably, DNA damage was highest for those babies carrying polymorphisms for certain biotransformation enzymes that can further affect whether carcinogens are activated or not. This review concluded that three biomarkers (plasma cotinine levels, DNA and protein adducts, and mutation frequency in a specific gene) allowed for: 1) the identification of sensitive sub-groups of newborns; and 2) more broadly, profound concern about such biomarkers in cord blood as being indicative of the potential for genotoxic effects in newborns of exposed mothers.

As introduced in Section 8.2 and the preceding section above, the continuing expansion of the field of epigenetics leads to the understanding that epigenetic mechanisms, (i.e., the manner in which heritable changes in gene expression and chromatin organization occur, independent of DNA), play a central role in the development of cancer. Thus, in a review[573] of epigenetics and cancer, the understanding of epigenetic mechanisms in healthy biological systems is described as aiding with the understanding of aberrant epigenetic patterns associated with disease, particularly cancer. Indeed, the author uses the term "epimutagen" to describe environmental and dietary factors that alter epigenetic patterns, providing an overall term for an expanded concept of mutagenesis and the many biomarkers that are being discovered within detailed investigations of epigenetic mechanisms in cancer. Across the literature, these aberrant patterns in epigenetic mechanisms include myriad biomarkers, depending on the biochemical effects that are associated with different exposures. This is a new and rapidly expanding field and the range and complexity of possible biomarkers is beyond the scope of this report.

In addition to biomarkers for genotoxic substances, including but not limited to the examples noted above, there are many other markers of epigenetic change for endocrine disrupting substances associated with cancer. In response, experts note[574] that the fields of epidemiology and toxicology need to be more highly integrated such that toxicologists could identify the biomarkers to be found in human serum that could be used in epidemiological studies to provide early identification of risks thus aiding in the identification of precursors of disease in human populations. Such efforts could occur sooner than more traditional approaches of awaiting and documenting excess disease or, indeed, other developmental or behavioural indicators of possible harm such as low birth weight, behaviour problems, etc. Hence, such biomarkers, particularly of the early stages of cancer, are increasingly important in understanding early life exposures, not least because they may contribute to efforts towards greater disease prevention.

12.4 Environmental Exposures of Concern

Similar to the chemical and/or pollution-related environmental risk factors for other chronic diseases discussed in this report, a very large number of substances are of concern for multiple cancers. There is also the daily reality of exposures to mixtures of many different substances.

Table 5 summarizes a large amount of data concerning links between cancer and various substances encountered in both occupational and environmental settings. The final two columns of the table note the specific types cancers for which the evidence of links to these substances is strongest. The fourth column indicates for each category of substance or agent the cancer types where evidence is deemed causal according to criteria applied by the International Agency for Research on Cancer (IARC). IARC identifies multiple categories in its assessment of the strength of cancer evidence. Those substances classified in Group 1 are considered to be known to cause cancer in humans. The fifth column outlines the cancer types where each given substance or agent is *suspected* of a causal link as summarized in the review conducted by the President's Cancer Panel.[575] That review notes suspected evidence of a causal link derived from: mixed results from epidemiologic studies; and positive findings from well-designed and conducted studies, including animal studies.

573 Herceg Z (2007) Epigenetics and cancer: towards an evaluation of the impact of environmental and dietary factors. *Mutagenesis*; 28(2):91-103.
574 Betts K (2007) interviewing Lynn Goldman (Johns Hopkins University; Blumberg School of Public Health) Perfluoroalkyl Acids – What is the Evidence Telling Us? *Environmental Health Perspectives;* 115(5):A250-56.
575 Reuben S for the President's Cancer Panel (2010) *op. cit.*

Table 5, adapted from the President's Cancer Panel report, notes a wide range of substances and agents with known or suspected human carcinogenicity. The following additional observations can be made about this table:

- The information about sources and uses of substances indicates that many different consumer products can be sources of known or suspected carcinogens.
- In addition to pesticides as an already large category of substances of concern, pesticide applications arise in other categories as well, including in the reactive chemicals, solvents, the "other" category, and for naphthalene, in the final row of substances recently declared "CEPA-toxic."
- Given the choice of noting only substances with either causal or suspected associations with cancer, it is important to note that less robust evidence exists for cancer associations for many additional substances not listed in Table 5, notably specific mention of substances suspected of endocrine disruption as discussed in detail below.
- All of the most prevalent cancers in the child and adult population, as well as those for which prevalence is increasing, appear in Table 5, often repeatedly, including cancers of the breast, prostate, lung, colorectum, bladder, testis, liver, thyroid, brain/central nervous system as well as leukemia, soft tissue sarcoma and lymphoma.

While Table 5 summarizes information about a wide range of exposures, it does not indicate specifically those that are of concern in terms of early exposures (in the womb or childhood) creating risk for cancer later in life. However, cancer is typically a disease of long latency. As discussed in the following section, exposures in early life can begin processes that can eventually lead to cancer and can also increase vulnerability to exposures that occur later in life.

12.4.1 Evidence for Greater Susceptibility to Early Environmental Exposures

Far greater scientific understanding exists for cancer in adults than in children because the evidence base is dominated by studies of either adult humans or sexually and physically mature laboratory animals. Nevertheless, there is scientific consensus that young animals are usually more susceptible to carcinogens than their adult counterparts[576] and indeed this risk can be about 10-fold greater than the risk of exposures of similar duration occurring later in life.[577] The U.S. Environmental Protection Agency summarizes extensive evidence about the greater susceptibility of children (inclusively defined to include pre-conception through adolescence) to carcinogens, in two risk assessment guidance documents,[578,579] as follows:

- Although some early-life exposures result in different tumours in children than in adults, generally the same tumour sites are observed following either perinatal or adult exposure to known carcinogens, indicating a similar mode of action.
- For several forms of cancer resulting from certain types of radiation the risk is highest following childhood exposure, e.g. cancers of the skin (UV radiation), breast and thyroid (ionizing radiation).
- Perinatal exposure to chemical carcinogens, in conjunction with adult exposure, usually increases the incidence of tumours or reduces the latent period before tumours are observed.
- Children have different capacity to metabolize and clear chemicals which can result in larger internal doses of carcinogenic agents.
- More frequent cell division during development can enhance the expression of mutations due to the reduced time available for cellular repair of DNA lesions. This more frequent cell division can also result in clonal expansion of cells with mutations from prior

576 McConnell EE (1992) Comparative response in carcinogenesis bioassay as a function of age at first exposure. In: Guzelian P et al (eds) *Similarities and difference between children and adults: implications for risk assessment*. Washington, DC: ILSI Press; pp. 66-78.
577 Ginsberg GL (2003) Assessing cancer risks from short-term exposures in children. *Risk Analysis;* 23(1):19-34.
578 U.S. Environmental Protection Agency (2005) *Guidelines for Carcinogen Risk Assessment*, EPA/630/P-03/001F.
579 U.S. Environmental Protection Agency (2005) *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. EPA/630/R-03/003F

Table 5: Summary of Environmental and Occupational Links with Cancer (adapted from the *President's Cancer Panel*, 2010)

Category	Carcinogenic Agent	Sources/Uses	Strong evidence of causal link (IARC Group 1)	Suspected evidence of causal link (Presidents Cancer Panel review)
Aromatic Amines	Benzidine, 2-naphylamine, 4,4'-methylenebis 2-chloraniline (MOCA), chlornaphazine, Heterocyclic Aromatic Amines	Rubber and cutting oil production, azo dye manufacturing, and used as pesticides. Common in chemical and mechanical industries and aluminum transformation. Found in tobacco smoke and widely used in textile industry and as hair dyes.	Bladder (Benzidine, 2-naphylamine, 4,4'-methylenebis 2-chloraniline (MOCA), chlornaphazine)	Prostate (Heterocyclic Aromatic Amines)
Chlorination By-Products	Trihalomethanes	Chloroform, bromodichloromethane and bromoform. (formed by interaction of chlorine and bromine with organic chemicals)	Bladder	Colorectum, Esophagus
Environmental Tobacco Smoke	Contains more than 50 known carcinogens	Combined release from burning end of tobacco products and exhaled smoke.	Lung, Breast	
Metals	Arsenic	By-product of non-ferrous metal production (mainly copper). Greater than 10% of dust in some smelter operations.	Bladder, Kidney, Lung, Skin, Soft Tissue Sarcoma (angiosarcoma of the liver)	Brain/Central Nervous System, Liver/Biliary, Prostate, Soft Tissue Sarcoma
	Beryllium	Nuclear, aircraft and medical devices industries. Alloy or in specialized ceramics for electrical and electronics applications. Contaminant of coal and fuel oil combustion.	Lung	
	Cadmium	Naturally occurring in zinc-, lead-, and copper-bearing ores. Stabilizer in polyvinyl chloride products, colour pigment, common in rechargeable nickel-cadmium batteries, pollutant in phosphate fertilizers.	Lung	Pancreas, Kidney, Prostate
	Chromium	Steel and other alloy production. Chromium III and Chromium IV used in chrome plating, manufacture of dyes and pigments, leather tanning, wood preserving.	Lung, Nasal/Nasopharynx	
	Lead	Batteries, ammunition, solder, pipes and X-ray shielding devices. Still in some gasoline, paints, ceramic products, caulking, and pipe solder but large reductions via regulation. Common in costume jewellery.		Brain/Central Nervous System, Lung, Kidney, Stomach
	Mercury	Production of chlorine gas and caustic soda. Thermometers, dental fillings, batteries. In some skin lightening creams and antiseptic creams and ointments. Transformed by microorganisms to methylmercury in water and soil.		Brain/Central Nervous System
	Nickel	Primarily as alloy in stainless steel. Nickel platting and batteries.	Lung, Nasal/Nasopharynx	Larynx, Pancreas, Stomach

Category	Carcinogenic Agent	Sources/Uses	Strong evidence of causal link (IARC Group 1)	Suspected evidence of causal link (Presidents Cancer Panel review)
Metalworking Fluids and/or Mineral Oils	Straight Oils, Soluble Oils, Synthetic and Semi-synthetic Fluids	Various industries including metal machining, print press operating, cotton and jute spinning	Bladder, Larynx, Lung, Nasal/Nasopharynx (mineral oils), Rectum, Skin, Stomach	Esophagus, Pancreas, Prostate
Natural Fibres/ Dust	Asbestos	Acoustical and thermal insulation.	Larynx, Lung, Mesothelioma, Stomach	
	Silica	Foundries, brick-making and sandblasting	Lung	
	Talc containing asbestiform fibres	Manufacturing of pottery, paper, paint and cosmetics	Lung	Ovary
	Wood dust	Carpentry, joinery, furniture and cabinetry	Lung, Nasal/Nasopharynx	Larynx
Pesticides	Herbicides, Fungicides, Insecticides	Preventing, destroying, repelling, mitigating pests. Plant regulators, defoliants, dessicants. Majority used in agriculture. Also residential applications.		Brain/Central Nervous System, Breast, Colon, Hodgkin Lymphoma, Leukemia, Lung, Multiple Myeloma, Non-Hodgkin's Lymphoma, Ovary, Pancreas, Kidney, Soft Tissue Sarcoma, Stomach, Testicle
Petrochemicals and Combustion By-Products	Petroleum Products, Motor Vehicle Exhausts (including diesel) Polycyclic Aromatic Hydrocarbons (PAHs), Soot, Dioxins	Petrochemicals derived from natural gas or petroleum and used to produce pesticides, plastics, medicines and dyes. Substances produced as building blocks for other products but mainly from incomplete combustion of coal, oil, gas (including diesel), household waste, tobacco and other organic substances. Dioxins produced as by-products of combustion of chlorine and carbon-based chemicals such as PVC plastics, and via chlorine-bleaching process for whitening paper and wood pulp.	Lung (PAHs, air pollution, including diesel exhaust, soot, dioxin), Non-Hodgkin Lymphoma (dioxin), Soft Tissue Sarcoma (dioxin), Skin (PAHs)	Bladder (PAHs, diesel exhaust), Breast (dioxin, PAHs), Esophagus (soot), Larynx (PAHs,), Multiple Myeloma (dioxin), Prostate (dioxin, PAHs)
Radiation	Ionizing Radiation	Several particle types released by radioactive material, high-voltage equipment, nuclear reactions, and stars. Particles of concern include alpha and beta particles, X-rays and gamma rays.	Bladder, Bone, Brain/ Central Nervous System, Breast, Colon, Leukemia, Liver/Biliary, Lung, Multiple Myeloma, Nasal and Nasopharynx, Ovary, Soft Tissue Sarcoma, Skin, Stomach, Thyroid.	

Category	Carcinogenic Agent	Sources/Uses	Strong evidence of causal link (IARC Group 1)	Suspected evidence of causal link (Presidents Cancer Panel review)
Radiation (cont'd)	Non-ionizing	Microwaves and electromagnetic frequencies, including radiowaves and extremely low-frequency electromagnetic fields		Brain, Breast, Leukemia, Salivary Gland
	Ultraviolet Radiation	Solar radiation from the sun	Skin	
Reactive Chemicals	Butadiene	Production of polymers for manufacture of styrene-butadiene rubber for tires; nitrile rubber for hoses, gaskets, adhesives, footwear; styreme-butadiene latexes for paints and carpet backing; acrylonitrile-butadiene-styrene polymers for parts, pipes and various appliances.		Leukemia
	Ethylene Oxide	Sterilant, disinfectant and pesticide. Ingredient in making resins, films and antifreeze.	Leukemia	Breast
	Formaldehyde	Production of urea, phenol or melamine resins for molded products such as appliances, electric controls and telephones. Also used in particle-board and in surface coatings.	Nasal/Nasopharynx	Leukemia
	Sulphuric Acid	Production of isopropanol, ethanol, treatment of metals, manufacture of soaps, detergents and batteries.	Larynx	Lung
	Vinyl Chloride	In polyvinyl resins for production of plastic pipes, floor coverings, and in electrical and transportation applications.	Liver/Biliary, Soft Tissue Sarcoma (angio-sarcoma of the liver)	
Solvents	Benzene	Intermediate in production of plastics, resins and some synthetic and nylon fibres. Used to make some types of rubbers, lubricants, dyes, detergents, drugs and pesticides. Also in crude oil, gasoline and cigarette smoke.	Leukemia, Multiple Myeloma, Non-Hodgkin Lymphoma	Brain/Central Nervous System, Lung, Nasal/ Nasopharynx
	Carbon Tetrachloride	Industrial applications. Before being banned, used in the production of refrigeration fluid and propellants for aerosol cans, as a pesticide, as a cleaning fluid and degreasing agent, in fire extinguishers, and in spot removers.		Leukemia
	Methylene Chloride	Solvent in industrial applications and as a paint stripper. In some aerosol and pesticide products and in production of photographic film.		Brain/Central Nervous System, Liver/Biliary
	Styrene	Production of rubber, plastic insulation, fiberglass, pipes, automobile parts, food containers and carpet backing.		Non-Hodgkin Lymphoma

Category	Carcinogenic Agent	Sources/Uses	Strong evidence of causal link (IARC Group 1)	Suspected evidence of causal link (Presidents Cancer Panel review)
Solvents (cont'd)	Toluene	Production of paints, paint thinners, fingernail polish, lacquers, adhesives and rubber. Some printing and leather tanning processes.		Brain/Central Nervous System, Lung, Colorectum
	Trichloro-ethylene (TCE)	Degreasing metal parts. Previously used in dry cleaning. May be found in printing inks, varnishes, adhesives, paints, and lacquers.	Liver/Biliary	Cervix, Hodgkin Lymphoma, Kidney, Leukemia, Non-Hodgkin Lymphoma
	Tetrachloro-ethylene (PCE)	Degreasing metal parts and industrial solvent. Dry cleaning.		Bladder, Cervix, Esophagus, Kidney, Non-Hodgkin Lymphona
	Xylene(s)	Cleaning agent, thinner for paint and in paints and varnishes. Used in printing, rubber and leather industries. Low levels in gasoline and airplane fuel.		Brain/Central Nervous System, Colorectum
Other	Creosotes	Includes coal tar and coal tar pitch formed via high temperature treatment of wood, coal, or from the resin of creosote bush. Coal tar products used in medicine, animal and bird repellants and as pesticides. Coal tar creosote widely used as wood preservative. Coal tar, coal tar pitch, and coal tar pitch volatiles using in roofing, road paving, aluminum smelting and coking.	Bladder (coal tars), Lung, Skin	
	Endocrine Disruptors	Several natural and synthetic chemicals capable of mimicking the body's natural hormones (see also detailed list at www.ourstolenfuture.org/Basics/chemlist.htm and related discussions in Section 12.5)	Breast (DES) Cervic (DES)	Breast (bisphenol A), Prostate (bisphenol A), Testicle (chlorinated insecticides)
	Hair Dyes	Hair colouring products – chemicals agents vary according to the colour and degree of dye permanency (temporary, semi-permanent, demi, and permanent).		Bladder, Brain/Central Nervous System, Leukemia, Multiple Myeloma, Non-Hodgkin Lymphoma
	Nitrosamines and N-nitroso Compounds	Formed when amines and nitrosating agents chemically react. Found in the rubber, metal and agricultural industries, and in cosmetics and foods such as fried bacon and cured meats.		Brain/Central Nervous System, Kidney
	Poly-chlorinated Biphenyls (PCBs)	Banned in the 1970s but still circulating in the environment – used as coolants and lubricants in transformers, capacitors, and other electrical equipment.	Liver/Biliary	Breast, Non-Hodgkin Lymphoma

unrepaired DNA damage.

- Some embryonic cells, such as brain cells, lack key DNA repair enzymes.
- Components of the immune system involved in response to carcinogens are not fully functional during development.
- Hormonal systems operate at different levels during different lifestages creating different periods of vulnerability to carcinogenic modes of action that are mediated through the endocrine system.
- Altered development or developmental abnormalities from perinatal exposures can result in a predisposition to carcinogenic effects later in life, including from exposure to other chemicals.

For children, the total lifetime environmental exposure to carcinogens represents a cancer threat simply because they have more years to live, allowing for greater likelihood for the expression of long latency diseases, such as cancer. While this greater opportunity for cancer to arise from chemicals with latent effects is intuitively obvious, the evidence (summarized above) points to a more complex set of issues. It is well-understood that cancer latency can span 20 to 40 years, that industrial activities result in multiple exposures to known or suspected carcinogens, and that we currently have an aging and therefore more cancer-susceptible, population. It is more clearly appreciated as well, that the timing of exposure also matters. Developmental windows of vulnerability can set in motion processes that can create a greater likelihood of cancer later in life and when exposures are prenatal, cancers may appear earlier in life.[580]

The role of endocrine disruption in early life is particularly important. In a review[581] of studies addressing the potential effects of a broad range of exogenous sources of estrogen, in natural or synthetic form (e.g., naturally in food or as hormones given to animals to promote growth), or as endocrine-disrupting substances, the authors make several conclusions about the greater vulnerability of children. They note that, despite scientific uncertainty, disrupted sex hormones likely play a role in current increasing incidences of testis, breast and prostate cancers as well as developmental impacts including genital abnormalities in boys and precocious puberty in girls. These experts conclude that children are extremely sensitive to exogenous sex steroids and endocrine disruptors with no apparent lower threshold below which hormonal effects in children and potentially severe effects in adult life, are not seen. Thus, they caution that unnecessary exposure of fetuses and children to such substances, even at very low levels, should be avoided.

Another review[582] of the literature looks at the evidence for *in utero* conditions affecting later cancer risk and finds that epidemiological and experimental data support the

hypothesis that factors acting *in utero* play a role in the development of cancer in the testis and breast while inconclusively pointing to links with other cancers in the prostate, urinary system and colorectum. In reviewing the possible mechanisms, they describe ongoing uncertainty but the likelihood of hormonal disturbances, number of cells at risk (i.e., the proportionally larger amount of cell division that occurs during *in utero* development) and genetic or epigenetic events.

Experts in endocrinology note[583] that the drug DES has become an important model for understanding endocrine disruption and the proof-of-principle for latent effects of *in utero* exposure to exogenous estrogenic compounds. Evidence about associations between cancer and early life exposure to endocrine disrupting substances is discussed further below.

580 This overall conclusion, captured in the U.S.EPA 2005 risk assessment guidance continues to be confirmed. See, e.g., Soffritti M et al (2007) Consequences of Exposure to Carcinogens Beginning During Developmental Life. MiniReview in *Basic and Clinical Pharmacology and Toxicology;* 102:118-124.

581 Aksglaede L et al (2006) The sensitivity of the child to sex steroids: possible impact of exogenous estrogens. *Human Reproduction Update*; 12:341-349.

582 Grotmol T et al (2006) Conditions in utero and cancer risk. *European Journal of Epidemiology*; 21:561-70.

583 Diamanti-Kandarakis E et al (2009) *op cit*.

12.5 Early Life Environmental Risk Factors for Three Common Cancers

As mentioned above, the most common and/or increasing cancers in the Canadian population are breast (women), prostate (men), lung and colorectal (both sexes), bladder (both sexes), thyroid (both sexes but higher in women, especially in young women), testicular and liver (men) and soft tissue sarcoma (young men). In children, the most common are leukemia, cancers of the brain and nervous system and lymphomas, with non-Hodgkin's lymphoma also rising among young adults, particularly young women. Across most of these cancers, varying levels of evidence are available for links to early environmental exposures (see, e.g., Table 5 above).

The following three subsections take a closer look at the evidence for early life exposure links to these three important cancers: breast, prostate and testicular.

12.5.1 Breast Cancer

While recognizing that the multiple and often interacting risk factors, i.e., genetic, behavioural and environmental, (as well as reproductive history in the case of breast cancer), discussed above are involved in any cancer, considerable evidence exists pointing to a very wide range of environmental exposures associated with breast cancer.

In its *Fifth State of the Evidence* review,[584] the Breast Cancer Fund (BCF) summarizes evidence from over 400 studies investigating links to breast cancer from exposure to ionizing radiation and diverse chemicals. In the BCF *Sixth State of the Evidence* review,[585] another 250 studies are reviewed, many of which examine the importance of 1) timing of exposures during early development, 2) low-dose, early life exposures at environmentally significant levels, 3) the reality of constant exposure to mixtures of environmental contaminants, and 4) the complexity of interacting risk factors for breast cancer.

Evidence about ionizing radiation causing breast cancer has been available since the aftermath of the atomic bombs of World War II[586] and nuclear accidents since that time, such as the Chernobyl[587] disaster in 1986. Evidence about the cancer risks of ionizing radiation also forms a significant part of the evidence for the greater vulnerability to breast and other forms of cancer if exposure occurs in early life. More recent research indicates a possible synergistic effect of radiation and endocrine disrupting chemicals in contributing to breast cancer.[588]

The BCF's two latest reviews divide the chemical exposures associated with breast cancer into those for which there is evidence of genotoxicity and those linked to endocrine toxicity, (recognizing that for some chemicals, there is evidence that both mechanisms can occur). Genotoxic substances include benzene, organic solvents other than benzene, vinyl chloride, 1,3-butadiene and ethylene oxide. Evidence for associations with breast cancer for these substances is primarily known from studying occupational exposure in adults, so they are not described in detail here. However, true to what is known about the greater vulnerability of the young to carcinogens, some studies indicate this vulnerability to mammary tumours from genotoxic substances in young laboratory animals, e.g., for some organic solvents and for 1,3-butadiene. Aromatic amines[589] and PAHs [590] are among the categories of substances for which there is evidence of both genotoxicity and endocrine disrupting mechanisms that link to breast cancer.

From both reviews, it is clear that, for early life exposures and breast cancer, the greatest risks appear to come from large categories of substances suspected of endocrine disruption, either as xenoestrogens (i.e., foreign estrogens) or via other endocrine disrupting properties. The

584 Breast Cancer Fund (2008) *State of the Evidence: The Connection Between Breast Cancer and the Environment*. Fifth edition. Gray J (ed.)
585 Breast Cancer Fund (2010) *State of the Evidence: The Connection Between Breast Cancer and the Environment*. Sixth edition. Gray J (ed.)
586 Land CE (1995) Studies of cancer and radiation dose among A-bomb survivors: The example of breast cancer. *Journal of the American Medical Association;* 274:402-407.
587 Pukkala E et al (2006) Breast cancer in Belarus and Ukraine after the Chernobyl accident. *International Journal of Cancer;* 119:651-658.
588 Calaf GM, Hei TK (2000). Establishment of a radiation-and estrogen-induced breast cancer model. *Carcinogenesis;* 21:769-776.
589 Gooderham NJ et al (2006) Mechanisms of action of the carcinogenic heterocyclic amine PhIP. *Toxicology Letters;* 168:269-277.
590 Pliskova M et al (2005).Deregulation of cell proliferation by polycyclic aromatic hydrocarbons in human breast carcinoma MCF-7 cells reflects both genotoxic and nongenotoxic events. *Toxicological Sciences*; 83:246-246.

plausibility of a link between endocrine disrupting substances and breast cancer arises from a large body of evidence showing associations between breast cancer and adult exposures to the natural hormones estrogen and progestins[591] as well as to hormone replacement therapy,[592] oral contraceptives[593] and to the drug DES with prenatal exposure to DES also associated with greater risk of breast cancer among daughters.[594,595] The association with elevated breast cancer risk is due to excess amounts of, in the first case, natural estrogen, and in the latter three, synthetic estrogen. For the large number of chemicals that exert an endocrine disrupting effect by mimicking or altering natural estrogen, experts have long believed that a similar carcinogenic effect is likely.[596]

Table 6 is adapted from the BCF *Sixth State of the Evidence* report and provides a list of compounds linked to breast cancer.

Table 6 notes the ratings for evidence of carcinogenicity established by the International Agency for Research on Cancer and the U.S. National Toxicology Program. Despite the fact that most substances on this table are linked to breast cancer due to evidence about endocrine disruption, neither of these agencies has yet to classify endocrine-disrupting substances as carcinogens. However, the Sixth BCF report points to new leadership in the U.S. within the Environmental Protection Agency, the Food and Drug Agency and the National Institute of Environmental Health Sciences, which is arguing that existing data point to the need for more research to improve science-based policy and regulatory decisions primarily with respect to improving the understanding of the health effects of exposures to endocrine disrupting compounds.

The strength of evidence for links to breast cancer varies considerably across the many substances noted in Tables 5 and 6 and some key issues and studies are highlighted below.

As reviewed in the BCF reports and another comprehensive review by the Silent Spring Institute,[597,598,599] evidence is available of endocrine disruption associations with breast cancer for most POPs including dioxins, PCBs, and most of the persistent OC pesticides including DDT, its metabolite, DDE, as well as dieldrin, aldrin, heptachlor and chlordane. Across these highly toxic substances, the evidence includes, for example, these chemicals inducing the proliferation of breast cancer cells *in vitro*, evidence of endocrine disruption in wildlife populations, limited epidemiological evidence, and a wide range of *in vivo* laboratory experiments, mostly in rodents.

Numerous methodological challenges exist, even for these relatively well-studied substances, in establishing such associations between early life exposure and cancers later in life. These challenges can include the large time lag between when early life exposure may initiate a carcinogenic process and when the disease occurs, the frequent inability to obtain accurate records of early life exposure, the ever-present reality of exposure to complex mixtures of low levels of substances, and many other variables as reviewed in Sections 3 and 7 above. Notably, despite these difficulties and controversy arising from how to interpret data about the effects of multiple xenoestrogens, assessments of total xenoestrogen exposure in fatty tissue correlate positively with breast cancer incidence.[600]

591 Russo J and Russo I (2004) Ch. 4: The role of estrogen in breast cancer. In: *Molecular Basis of Breast Cancer.* Springer-Verlag:Berlin.

592 Krieger N etal (2005).Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. *Journal of Epidemiology and Community Health;* 59(9):740-748.

593 Deligeroroglou E et al (2003).Oral contraceptives and reproductive system cancer. *Annals of the NewYork Academy of Sciences;* 997:199-208.

594 Titus-Ernstoff L et al (2001). Long-term cancer risk in women given diethylstilbestrol (DES) during pregnancy. *British Journal of Cancer;* 84(1):126-133.

595 Troisi Ret al (2007). Cancer risk in women prenatally exposed to diethylstilbestrol. *International Journal of Cancer;* 121:356-360.

596 Davis DL et al (1993) Medical hypothesis: Xenoestrogens as preventable causes of breast cancer. *Environmental Health Perspectives;* 101(5):371-377.

597 Rudel RA et al (2007) Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention.*Cancer;* 109 (*Suppl 12*) 2635-2666.

598 Brody JG et al (2007) Environmental pollutants and breast cancer: Epidemiologic studies *Cancer;* 109 (*Suppl* 12): 2667-2711.

599 See also: Rudel RA et al (2011) Environmental Exposures and Mammary Gland Development: State of the Science, Public Health Implications, and Research Recommendations. Environmental Health Perspectives; e-pub ahead of print: 22 June 2011. http://dx.doi.org/10.1289/ehp.1002864

600 Ibarluzea JM et al (2004) Breast cancer risk and the combined effect of environmental estrogens. *Cancer Causes and Control;* 15:591-600.

Table 6: Endocrine-Disrupting Compounds Linked to Breast Cancer with IARC and NTP Ratings Noted (adapted from Breast Cancer Fund, 2010, 6th State of the Evidence Review)

	International Agency for Research on Cancer			United States National Toxicology Program		Endocrine Disrupting Compound
Compounds Linked to Breast Cancer	**Known**	**Probable**	**Possible**	**Known**	**Reasonably Anticipated**	
Hormones: Pharmaceuticals and Personal Care Products						
Hormone Replacement Therapy (HRT) and oral contraceptives	•			•		
Diethylstilbesterol (DES)	•			•		
Estrogens and placental hormones in personal care products	•			•		
Xenoestrogens and Other Endocrine-Disrupting Compounds (EDCs)						
Bisphenol A						•
Phthalates						•
Parabens						•
Alkylphenols						•
Polycyclic aromatic hydrocarbons (PAHs)		•			•	•
Pesticides and Herbicides						•
Triazine herbicides: Atrazine						•
Heptachlor			•			•
Dieldrin and aldrin						•
DDT/DDE			•	•		•
Other pesticides						•
Polybrominated diphenyl ether (PBDE) flame retardants						•
Dioxins	•			•		•
PCBs		•				•
Aromatic amines		•				•
Sunscreens (UV filters)						•
Tobacco smoke (active and passive exposures)	•			•		•
Metals	•			•		•
Hormones in Food: Natural and Additive						
Phytoestrogrens						•
Zeranol (Ralgro)						•
Recombinant bovine somatotropin (rBST)						•
Non-Endocrine Disrupting Industrial Chemicals						
Benzene	•			•		
Organic solvents other than benzene		•			•	
Vinyl chloride	•			•		
1,3-butadiene		•		•		
Ethylene oxide	•			•		

A small but unique epidemiological study[601] seeking to investigate the link between early life DDT exposure and breast cancer helps illustrate the importance of overcoming some of these challenges to assess periods of vulnerability to breast carcinogens. This prospective, nested case-control study used serum samples that were obtained between the years 1959 and 1967, a time of heavy DDT use in the U.S., from young adult U.S. women who had recently given birth. (Note that serum measures of DDT and its metabolites are indicative of recent exposure.) The researchers noted a five-fold greater risk of breast cancer for women born after 1931, linked to higher serum measures of DDT exposure. These women were under the age of 14 in 1945 when widespread DDT use began and mostly under age 20 as DDT use peaked. The key periods of vulnerability in breast tissue to environmental exposures are during fetal life, adolescence and early reproductive life. Women not exposed to DDT before age 14 (i.e. born in 1931 or earlier, therefore older when peak DDT use occurred) showed no increased risk of breast cancer associated with DDT exposure.

Despite many of these substances having been banned or severely restricted (e.g., controls on dioxins and bans on PCBs and most of the OC pesticides) their persistence in the environment means exposure continues. As well, their intensive use in the decades since World War II likely contributed to widespread early life exposures among those experiencing the current high prevalence of breast cancer.

Similar evidence of xenoestrogenic activity exists for additional pesticides. Among the triazine herbicides (atrazine, simazine, propazine and cyanazine) all have been shown to induce mammary cancer in laboratory rats.[602] These chemicals are among the most heavily used herbicides in agriculture with atrazine as the most extensively studied for associations with breast cancer.

Considerable wildlife and laboratory research in multiple species (fish, amphibians, reptiles and rodents) confirms the endocrine-disrupting effects of the pesticide atrazine.[603] *In vitro* experiments in human and carp cells,[604] and in rodents, [605] show that atrazine increases the activity of aromatase, an enzyme that serves to convert other hormones to estrogen. Oncologists already know of the importance of this enzyme in the development of breast cancer since they use drugs to block aromatase activity when treating breast cancer. Additional rat studies show that atrazine exposure during gestation has long-term impacts including delaying mammary gland development at puberty, extending the window of vulnerability to breast carcinogens,[606] and developmental abnormalities that persist into adulthood in the breast tissue of pups exposed *in utero*.[607]

Animal studies of the endocrine-disrupting properties of BPA, one of the most widely used chemicals in modern life, also show associations with breast cancer. BPA exposure is ubiquitous with evidence of contamination in air, water, sediments, industrial waste water and sewage sludge, and house dust.[608,609] Although it is not highly persistent, this widespread contamination and its use in myriad consumer products results in what is called "quasi-persistence." Nearly 100% of biological samples show detectable levels of BPA including in breast milk,[610] cord blood,[611] amniotic

601 Cohn et al. (2007) DDT and breast cancer in young women: new data on the significance of age at exposure. *Environmental Health Perspectives*; 115:1406–1414.
602 O'Connor JC et al (2000). Role of prolactin in chloro-S-triazine rat mammary tumorigenesis. *Drug and Chemical Toxicology;* 23:575-601.
603 U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (2003) *Toxicological Profile for Atrazine*.
604 Sanderson JT et al (2001) Effects of chloro-S-triazine herbicides and metabolites on aromatase activity in various human cell lines and on vitellogenin production in male carp hepatocytes. *Environmental Health Perspectives;* 109:1027-1031.
605 Fan W et al (2007) Atrazine-Induced Aromatase Expression Is SF-1 Dependent: Implications for Endocrine Disruption in Wildlife and Reproductive Cancers in Humans. *Environmental Health Perspectives;* 115(5):720-727.
606 Raynor JL et al (2005). Adverse effects of prenatal exposure to atrazine during a critical period of mammary gland growth. *Toxicological Sciences;* 87:255-266.
607 Enoch RR et al (2007).Mammary gland development as a sensitive endpoint after acute prenatal exposure to an atrazine metabolite mixture in female Long Evans rats. *Environmental Health Perspectives;* 115:5541-547.
608 Environment Canada, Health Canada (2008) Screening Assessment for the Challenge: Phenol, 4,4'-(1-methylethylidene)bis- (Bisphenol A)
609 Rudel RA et al (2003) Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine disrupting compounds in indoor air and dust. *Environmental Science and Technology;* 37:4543-4553.
610 Ye X et al (2006) Measuring environmental phenols and chlorinated organic chemicals in breast milk using automated on-line column-switching-high performance liquid chromatography-isotope dilution tandem mass spectrometry. *Journal of Chromatography B*; 831(0):110-115
611 Schonfelder G et al (2002) Parent Bisphenol A accumulation in the human maternal-fetal-placental unit. *Environmental Health Perspectives;* 110:A703-A707.

fluid,[612] and human urine biomonitoring.[613,614,615] These studies also indicate significantly higher BPA levels in women, and higher levels still in children and fetuses. Recent research is challenging some previously held assumptions about human exposure and pharmacokinetics (or metabolism) of BPA. Research suggests for example that total daily human exposure is likely via multiple routes and also likely much higher than previously thought, that food may not be the only relevant and significant source of exposure to BPA, that non-oral (i.e dermal) exposure may be significant, and that the half-life of BPA in humans is longer than expected.[616,617]

Much is published about the suspected fetal origins of breast cancer resulting from the effects of xenoestrogens, including BPA. Specifically, experts[618] describe the potential for these substances to exert permanent epigenetic changes (during mammary gland development *in utero*) that alter later susceptibility, often before and during puberty, to other factors that can initiate breast cancer. These other factors can be, for example, increased vulnerability in breast epithelial cells for malignant transformation. This complex, multi-step situation may explain the inconsistencies in the findings from epidemiological and rodent studies. While rodent studies are increasingly elucidating this complex series of events beginning *in utero*, some epidemiological studies find associations between serum levels of suspected xenoestrogens at the time of breast cancer detection while others do not. In a review[619] about developmental exposures to multiple xenoestrogens, the authors note that rodent studies focused on critical periods of mammary development demonstrate a series of effects that can lead to breast cancer. The results of case-control epidemiological studies are less consistent but also largely lack the ability to evaluate exposures when critical early breast development was occurring in women diagnosed with breast cancer.

Using BPA as a case study, another review[620] of the suspected fetal origins of breast cancer looks at the large number of rodent studies of low-dose, *in utero* BPA exposure, describing the organizational and functional changes in mammary cells and tissue that arise at different developmental stages. The authors posit the results as the functional equivalent to the known risk factor of elevated estrogen in human breast cancer. As noted above for other xenoestrogens, these authors state that these multiple results in rodents buttress the link between fetal BPA exposure and breast cancer and support the hypothesis that exposure to BPA and other xenoestrogens may contribute to the increased incidence of breast cancer over the past five decades.

The BCF *State of the Evidence* reviews also describe the more limited evidence in the literature for links to breast cancer risk from early life exposure to alkylphenols, several metals, phthalates, parabens, UV filter components of sunscreens and the food additives bovine somatotropin (rBST) and zeranol. This evidence is generally from *in vitro* studies confirming xenoestrogenic activity and a small number of *in vivo* rodent studies showing increased risk of mammary cancer.

Finally, the conclusions in the BCF reviews concerning breast cancer risk from a much broader range of substances are echoed in the above-noted review[621] of endocrine-disrupting compounds and mammary gland development. The author notes that while little information exists about effects in human or rodent mammary tissue for several classes of environmental contaminants, these substances are otherwise known to alter endocrine hormone levels in ways that could affect either mammary development or result in tumours. These classes of compounds

612 Ikezuki Y et al (2002) Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Human Reproduction;* 17(11):2839–2841.

613 Calafat AM et al (2005) Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environmental Health Perspectives;* 113:391-395.

614 Centers for Disease Control and Prevention (2009) *Fourth National Report on Human Exposure to Environmental Chemicals*.

615 Bushnik T et al (2010) Lead and bisphenol A concentrations in the Canadian population. *Health Reports;* 21(3):7-18. Statistics Canada Catalogue no. 82-003-XPE.

616 Taylor JA et al (2011) Similarity of Bisphenol A Pharmacokinetics in Rhesus Monkeys and Mice: Relevance for Human Exposure. *Environmental Health Perspectives*; 119:422–430.

617 Stahlhut RW et al (2009) Bisphenol A data in NHANES suggest longer than expected half-life, substantial non-food exposure, or both. *Environmental Health Perspectives*; 117:784-789.

618 Hilakivi-Clarke L and de Assis S (2006) Fetal origins of breast cancer. *Trends in Endocrinology and Metabolism;* 17(9):340-348.

619 Fenton SE (2006) Endocrine-Disrupting Compounds and Mammary Gland Development: Early Exposure and Late Life Consequences. *Endocrinology;* 147(6) (*Suppl*):S18-S24

620 Soto AM et al (2008) Does Breast Cancer Start in the Womb? *Basic and Clinical Pharmacology and Toxicology;* 102:125-133.

621 Fenton (2006) *op. cit*.

include perchlorates, phthalates, perfluorinated alkyl acids, water disinfection by-products, alkylphenols, other heavy metals and brominated flame retardants (BFRs). These conclusions about links between early life exposure to endocrine disrupting compounds and breast cancer are similarly reached by experts in endocrinology who state that collectively, the large number of epidemiological and experimental studies point to endocrine disruptors altering mammary gland morphogenesis with the resulting dysgenic gland becoming more prone to the development of cancer.[622]

12.5.2 Prostate Cancer

Known prostate cancer risk factors include age and race (with African-American men having the highest incidence) as well as genetics (or family history of the disease). Other possible risk factors include: 1) diet (including high calorie, high fat, inadequate supply of key nutrients and interactions among other nutrients); 2) inactivity and abdominal obesity; 3) concomitant medical conditions (such as acromegaly related to imbalance in pituitary hormone secretion); and, 4) endogenous hormones including interactions among them and with the environment. This review of risk factors notes the need for more research to understand prostate cancer risk in several areas, key among them being greater understanding of interactions among several dietary factors, interactions among several endogenous hormones as well as gene-environment interactions in hormone synthesis, action, and metabolism.[623]

Across the evidence about known and potential risk factors among adult men, there is solid scientific evidence that hormones play a fundamental role in the initiation and progression of prostate cancer. Notably, in addition to evidence for androgens, human and animal evidence indicates that chronically elevated estrogens are associated with prostate cancer, information which supports the use of antiandrogens and antiestrogens in therapeutic treatment of the disease.[624] The clear role of hormones in prostate cancer underscores the need to better understand the potential risks of endocrine disrupting substances.

For chemical exposures in the environment there is evidence of associations of prostate cancer with occupational exposure to multiple pesticides, several of which are plausibly related to either endocrine disruption mechanisms or gene-environment interactions, though causal associations have not been established.[625,626,627] Additional occupational and environmental exposures have been associated with prostate cancer risk, also via endocrine-disrupting modes of action, including in robust occupational exposure evidence for PCBs,[628,629] some epidemiological evidence for arsenic,[630,631] and more limited and/or inconsistent evidence for occupational exposures to cadmium.[632]

Evidence highlighting links to prostate cancer from early life exposure to known endocrine disrupting substances includes the use of synthetic hormones in food production, the drug DES and the very similar chemical BPA, as discussed further below.

Animal and human evidence indicates associations between DES exposure *in utero* and prostate abnormalities linked to increased susceptibility to adult-onset prostate cancer. Moreover, similar to environmental estrogens, developmental exposure to DES exhibits a biphasic dose-response

622 Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):293-342.

623 Gann PH (2002) Risk factors for prostate cancer. *Reviews in Urology*; 4(*Suppl* 5):S3–S10

624 As reviewed in: Diamanti-Kandarakis E et al (2009) *op cit*.

625 Van Maele-Fabry G et al (2006) Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. *Cancer Causes and Control;* 17(4):353–373

626 Alavanja MC et al (2003) Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *American Journal of Epidemiology;* 157(9):800–814

627 Alavanja MCR et al (2004) Health Effects of Chronic Pesticide Exposure: Cancer and Neurotoxicity. *Annual Review of Public Health*; 25:155-197.

628 Hardell L et al (2006) Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *Journal of Occupational and Environmental Medicine*; 48:700–707.

629 Prince MM et al (2006) Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environmental Health Perspectives*; 114:1508–1514.

630 Chen CJ et al (1988) Arsenic and cancers. *Lancet;* 1:414–415

631 Lewis DR et al (1999) Drinking water arsenic in Utah: a cohort mortality study. *Environmental Health Perspectives*; 107:359–365.

632 Parent ME and Siemiatycki J (2001) Occupation and prostate cancer. *Epidemiological Reviews*; 23:138–143.

for several effects, including in the prostate, such that low-dose fetal exposure results in different effects on the prostate than higher doses. In a literature review[633] these experts note that this differential response in the prostate to low versus high doses of DES and other endocrine disrupting compounds must be recognized to ensure that a lack of a response at high doses is not interpreted as a lack of negative effects at low, environmentally relevant doses.

A similar biphasic or non-monotonic dose-response is apparent with bisphenol A, a chemical that is very similar to DES both in terms of chemical structure and known or suspected endocrine disruption effects. Alongside the findings of links to breast cancer, described in the previous section, *in vivo* and *in vitro* studies, including in the latter, studies in human cell cultures, indicate associations between prenatal and neonatal BPA exposure and alterations in prostate growth and development that may lead to later life prostate cancer.

For example, the above-cited review of developmental estrogen exposure in multiple rodent studies, combined with epidemiological evidence for the drug DES, concluded that a fetal basis may exist for prostate cancer. These investigators conducted a range of experiments to isolate high and low dose effects of DES, estradiol (natural estrogen) and BPA, as well as other synthetic estrogenic compounds, thereby testing a BPA dose typical of current environmental exposure. Across the doses tested, their results suggest that estrogen and xenoestrogen exposure during critical periods of prostate development results in an increased incidence and susceptibility to prostate cancer in the aging male with epigenetic mechanisms appearing to be responsible.[634]

Another review[635] by the U.S. National Institutes of Health and the U.S. Environmental Protection Agency evaluated the evidence for carcinogenicity of BPA including looking in detail at several ongoing areas of controversy related to the conduct of experimental studies. These experts concluded with confidence that BPA at low doses (i.e., at environmentally relevant concentrations) acts as an endocrine disruptor with some estrogenic properties, among other hormonal activities. They also considered it inconclusive but likely that "early life exposure to BPA may induce or predispose to preneoplastic lesions of the mammary gland and prostate gland in adult life." They also considered it possible that, in advanced prostate cancers with androgen receptor mutations, BPA may promote tumor progression and reduce time to recurrence.

Experts continue to disagree, some supporting, others contesting, around these and other conclusions in this review and in several other reviews.[636,637,638,639]

A more recent review[640] of BPA toxicology conducted by 21 experts in the field concludes from recent BPA studies that sufficiently robust environmental toxicology data point to the potential for adverse effects of endocrine disrupting compounds on human development.

Finally, in a study[641] seeking to resolve controversy about different dosing techniques used in animal studies, investigators found that rats prenatally exposed to BPA by two different routes (oral and subcutaneous injection), at levels similar to those observed in humans, had nearly identically heightened sensitivity to prostate cancer as adults. These authors conclude that these findings on prostate health are of direct relevance to humans at current BPA exposure levels.

633 Prins GS et al (2007) Developmental estrogen exposures predispose to prostate carcinogenesis with aging. *Reproductive Toxicology;* 23:374-382.
634 Ho SM et al (2006) Developmental exposure to estradiol and bisphenol A increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant 4. *Cancer Research*; 66:5624-5632.
635 Keri RA (2007) An evaluation of evidence for the carcinogenic activity of bisphenol A. *Reproductive Toxicology*; 24:240-252.
636 Maffini MV et al (2006) Endocrine disruptors and reproductive health: The case of bisphenol-A. *Molecular and Cellular Endocrinology*; 254:179-186.
637 vom Saal FS et al (2007) Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure. *Reproductive Toxicology*; 24:131–138.
638 National Toxicology Program – Center for the Evaluation of Risks to Human Reproduction (2008) *Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A*, NIH Publication No. 08-5994, September 2008.
639 European Food Safety Authority (2008) Toxicokinetics of Bisphenol A, Scientific Opinion of the Panel on Food additives, Flavourings, Processing aids and Materials in Contact with Food, Adopted 9 July 2008, *The European Food Safety Authority Journal*, 2008.
640 Vandenberg LN et al (2009) Bisphenol-A and the Great Divide: A Review of Controversies in the Field of Endocrine Disruption. *Endocrine Reviews*; 30(1):75-95.
641 Prins GS et al (2010) Serum bisphenolA pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague–Dawley rats. *Reproductive Toxicology*; 31(1):1-9.

12.5.3 *Testicular Cancer*

Testicular cancers, and more specifically the most common form, testicular germ cell cancers (TGCC), occur primarily among young men between the ages of 20 to 45. As noted in Section 12.1 above, in industrialized countries worldwide, including Canada, incidence has been rising over the last three to four decades, although large scale geographical differences exist for incidence of this disease.[642]

Studies of the etiology of testicular cancer indicate that while it has multiple risk factors, it is also a disease with early life origins, including from environmental exposures. Maternal and gestational risk factors have been variously (though inconsistently) identified in epidemiological studies to include low parity, low gestational age, maternal epilepsy and retained placenta,[643] as well as birth order, gestational duration, birth weight, maternal age and nausea during pregnancy. The more established risk factors include cryptorchidism (undescended testicles), carcinoma in situ (i.e., non-invasive) cells developed *in utero*, and *in utero* exposure to estrogens.[644,645] Additional established risk factors for testicular cancer include prior diagnosis, and family history, of TGCC, and there are inconsistent but likely weak associations with maternal smoking.[646]

Two reviews[647,648] of evidence about effects of *in utero* exposure to endocrine disrupting substances conclude that, despite scientific uncertainty, epidemiological and experimental data support the hypothesis that disrupted sex hormones likely play a role in current increasing incidence of testis cancer and genital abnormalities in boys.

A review[649] of genetic and environmental risk factors notes that TGCC etiology remains largely unknown but that exposures acting prenatally are instrumental, and while no specific exposures can be identified with certainty, there are associations with estrogens and estrogenic substances. This review also notes that evidence indicates puberty is another window of vulnerability when environmental factors may increase the risk of testicular cancer. Evidence for additional postnatal risk factors, and correlates, described by these reviewers include early puberty, sub-fertility, very tall adult stature (an indicator of nutritional intake) and consumption of dairy products during puberty. Added to the knowledge of established risk factors noted above, this broad spectrum of risk factors also leads these authors to conclude there is need for investigation of main effects as well as interactions among prenatal, genetic, and postnatal factors.

Given the strong evidence suggesting that TGCC originates during fetal development,[650] there are obvious methodological challenges in being able to evaluate whether and which environmental exposures may have been involved up to 30 or more years prior to the disease being diagnosed. Hence, epidemiological evidence for associations with environmental exposures is quite limited. For the drug DES, a potent estrogenic compound, evidence is strongest for other cancers but DES has also been linked to testicular cancer[651] and an increased risk of cryptorchidism,[652] itself a risk factor for testicular cancer, as noted above.

Studies investigating other endocrine disrupting substances have also found that, compared to mothers of men without testicular cancer, the mothers of testicular cancer patients had higher

642 Bray F et al (2006) Interpreting the international trends in testicular seminoma and nonseminoma incidence. *Nature Clinical Practice. Urology*; 3, 532–543.
643 Aschim EL et al (2006) Risk factors for testicular cancer—differences between pure non-seminoma and mixed seminoma/non-seminoma? *International Journal of Andrology*; 29:458-67.
644 Garner MJ et al (2005) Epidemiology of testicular cancer: an overview. *International Journal of Cancer;* 116, 331–339.
645 Baik I et al (2005) Association of fetal hormone levels with stem cell potential: Evidence for early life roots of human cancer. *Cancer Research*; 65:358-363.
646 McGlynn KA et al (2006) Maternal smoking and testicular germ cell tumors. *Cancer Epidemiology, Biomarkers and Prevention*; 15(10):1820-1824.
647 Aksglaede L et al (2006) *op cit*.
648 Grotmol T et al (2006) *op. cit.*
649 Richiardi L et al (2007) Genetic and environmental risk factors for testicular cancer. *International Journal of Andrology*; 30:230-241.
650 Almstrup K et al (2005) Genomic and Gene Expression Signature of the Pre-Invasive Testicular Carcinoma in Situ. *Cell Tissue Research*; 322:159-165.
651 Strohsnitter WC et al (2001) Cancer risk in men exposed in utero to diethylstilbestrol. *Journal of the National Cancer Institute;* 93:545–551.
652 Gill WB et al (1979) Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. *Journal of Urology;* 122:36–39.

blood concentrations of certain POPs including PCBs,[653] hexachlorobenzene and certain chlordane pesticides.[654] Another study[655] found associations between TGCC and increased exposure to DDE, the metabolite of the persistent OC pesticide DDT, as well as to chlordane (another OC pesticide) and its metabolites. In light of evidence for associations between these and other POPs and testicular cancer, a recent ecological study[656] compared Finland and Denmark for breast milk levels of POPs and incidence of testicular cancer. Danish breast milk samples had significantly higher levels of POPs (including dioxins, PCBs and the OC pesticides hexachlorobenzene and dieldrin) than samples from Finland. There is also a three- to four-fold higher incidence in Denmark of the male birth defects cryptorchidism and hypospadias (discussed further below) and testicular cancer. These authors see their findings as reinforcing the view that environmental exposure to endocrine disrupting chemicals may help to explain the temporal and between-country differences apparent in the incidence of male reproductive disorders. Notably, other studies show that the risk of testicular cancer among immigrants tends to match that of the host country population by the second generation indicating a role for environmental risk factors.[657,658]

12.5.3.1 *Testicular Dysgenesis Syndrome*

In addition to the evidence of links between environmental exposures and testicular cancer, a broader range of risk factors, including environmental exposures, are involved in the etiology of the developmental disorder called testicular dysgenesis syndrome (TDS), a hypothesis first described in 2001.[659] These experts in endocrinology proposed that testicular cancer should be combined with three other reproductive and developmental outcomes in males that have a common origin in fetal life. TDS encompasses impaired semen quality, the birth defects cryptorchidism (undescended testicles) and hypospadias, (a birth defect in the male urinary tract), as well as testicular cancer. These researchers also propose that expression of TDS varies along a spectrum such that those with mild forms have only one symptom, whereas those with more severe forms have three or four symptoms of the syndrome.[660] This hypothesis is supported by numerous animal studies but human epidemiological evidence remains limited and in some cases contradictory.[661,662,663] Moreover, endocrine disruption is seen as only one of multiple likely causes of TDS.

As a unifying hypothesis, TDS invokes a common origin for a cascade of effects flowing from initial deficient production or action of the hormone androgen during fetal testis development. The result is alteration in organization of three different cell types in the testis during fetal development (dysgenesis) that can then contribute to the two birth defects noted above, to compromised function in the fetal and mature testis, and also to testicular cancer.[664] A recent review[665] of the evidence for a fetal origin of testicular cancer as part of the TDS also concludes that the evidence points to fetal dysgenesis of the testis as an important precursor to testicular cancer. The result, to which they attribute a combination of genetic and environmental factors, is disturbed signalling

653 Hardell L et al (2004) Concentrations of polychlorinated biphenyls in blood and the risk for testicular cancer. *International Journal of Andrology*; 27:282-290.

654 Hardell L et al (2003) Increased concentrations of polychlorinated biphenyls, hexachlorobenzene, and chlordanes in mothers of men with testicular cancer. *Environmental Health Perspectives;* 111:930–934.

655 McGlynn KA et al (2008). Persistent organochlorine pesticides and risk of testicular germ cell tumors. *Journal of the National Cancer Institute*; 100(9):663-71.

656 Krysiak-Baltin K et al (2010) Country-specific chemical signatures of persistent environmental compounds in breast milk *International Journal of Andrology*; 33:270–278.

657 Myrup C et al (2008) Testicular cancer risk in first- and second-generation immigrants to Denmark. *Journal of the National Cancer Institute*; 100(1): 41.-7.

658 Hemminki K and Li X. (2002) Cancer risks in Nordic immigrants and their offspring in Sweden. *European Journal of Cancer*; 38:2428–2434.

659 Skakkebæk NE et al (2001) Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Human Reproduction;* 16:972–978.

660 Jørgensen N et al (2010) Testicular dysgenesis syndrome comprises some but not all cases of hypospadias and impaired spermatogenesis. *International Journal of Andrology;* 33:298-303.

661 Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):290-342.

662 Thorup J et al (2010) What is new in cryptorchidism and hypospadias—a critical review on the testicular dysgenesis hypothesis. *Journal of Pediatric Surgery*; 45:2074–2086.

663 Jurewicz J and Hanke W (2011) Exposure to Phthalates: Reproductive Outcome and Child Health. A review of Epidemiological Studies. *International Journal of Occupational Medicine and Environmental Health*; 24(2):115-141.

664 Sharpe RM and Skakkebaek NE (2008) Testicular dysgenesis syndrome: mechanistic insights and potential new downstream effects. *Fertility and Sterility;* 89 (2 Suppl):e33-8.

665 Sonne SB et al (2010) Review: Testicular dysgenesis syndrome and the origin of carcinoma in situ. *International Journal of Andrology*; 31:275-287.

between cells in the fetal testis allowing embryonic cells to survive in the pre-pubertal and adult testis. It is thus postulated that further aberrant hormone signalling during the prepubertal and post-pubertal periods leads to the accumulation of genetic changes in these surviving embryonic cells which then contributes to adult cancer.

Multiple animal studies demonstrate these effects occurring as a result of prenatal exposure to phthalates, and other endocrine-disrupting substances with anti-androgenic action. For example, one study showed undescended testis, penile abnormality and poor spermatogenesis associated with exposure to mixtures of several phthalates.[666] Other researchers have looked at mixtures of seven different substances – four pesticides and three phthalates – all seven known to disrupt androgen signalling. Several different mixtures of these chemicals induced reproductive tract malformations in rats in a cumulative, dose-additive manner.[667] Human studies are limited. In one recent British case-control study, pregnant women exposed to phthalates at work had a higher risk of bearing male children with hypospadias.[668] There is also epidemiological evidence for a link between residency near agricultural areas and/or direct parental exposure to endocrine-disrupting pesticides and hypospadias and cryptorchidism.[669]

For links to TDS and other health outcomes, there is ongoing uncertainty about the many possible mechanisms of endocrine disrupting chemicals including whether they act in the body like hormones themselves or whether they perturb endogenous hormones in diverse ways such as upsetting the action of individual hormones or the balance that exists between two or more of them.[670] Some substances, such as BPA, also appear to exert multiple endocrine disrupting properties.[671]

As the evidence base in this highly complex field continues to grow, it is prudent to compare analogous results in more robust areas of investigation with those less well studied. For example, there is strong evidence from animal studies indicating the antiandrogenic activity of phthalates, with the effect that two endogenous hormones, (insulin-like growth factor 3 and testosterone), are suppressed, an alteration that is directly associated with clinical features of TDS, including cryptorchidism and impaired spermatogenesis.[672,673] Such hormonal alterations generate reason for concern when other substances appear to alter endogenous hormone levels by similar, other, or as yet unknown, mechanisms.

For example, in research[674] exploring so-called "emerging endocrine disruptors," experts note that perfluorochemicals act as endocrine disruptors in adult rats by decreasing testosterone levels. Various effects occur at the cellular level manifesting in reduced testis function similar to that seen in TDS leading these experts to raise the question that if these chemicals can induce these effects in adults, what happens if a man with a moderately reduced testis function, perhaps caused by TDS induced *in utero*, is exposed as an adult to chemicals that can elicit the same effect.

In another example, for BPA, animal studies indicate that prenatal exposure results in permanent alterations of the morphology, tissue architecture, and cell proliferation control in the prostate and other androgen-target tissues leading to a conclusion that the individual thus exposed and affected prenatally may be predisposed to disease in adult life.[675] While this BPA evidence is stronger for negative impacts on sperm production and for prostate cancer (as discussed above),

666 Sharpe RM (2008) "Additional" effects of phthalate mixtures on fetal testosterone production. *Toxicological Sciences;* 105, 1–4.
667 River CV et al (2008) A mixture of seven antiandrogens induces reproductive malformations in rats. *International Journal of Andrology*; 31:249-262.
668 Ormond G et al (2009) Endocrine disruptors in the workplace, hair spray, folate supplementation and risk of hypospadias: case control study. *Environmental Health Perspectives;* 117(2):303-307.
669 As reviewed in: Diamanti-Kandarakis E et al (2009) Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. *Endocrine Reviews;* 30(4):290-342.
670 Sharpe RM (2003) The 'oestrogen hypothesis' – where do we stand now? International Journal of Andrology; 26:2–15.
671 Soto AM et al (2009) Interpreting endocrine disruption from an integrative biology perspective. *Molecular and Cellular Endocrinology*; 304 (2009) 3–7.
672 Ge R-S et al (2007) Phthalate ester toxicity in Leydig cells: Developmental timing and dosage considerations. *Reproductive Toxicology*; 23:366–373.
673 Howdeshell KL et al (2008) Mechanisms of action of phthalate esters, individually and in combination, to induce abnormal reproductive development in male laboratory rats. *Environmental Research*; 108(2):168–76.
674 Jensen AA and Leffers H (2009) Emerging endocrine disrupters: perfluoroalkylated substances. *International Journal of Andrology*; 31:161-169.
675 Maffini MV et al (2006) Endocrine disruptors and reproductive health: The case of bisphenol-A. *Molecular and Cellular Endocrinology*; 254:179-186.

experts believe there may be links to testicular cancer as well. Animal evidence indicates that very low doses of BPA (i.e., at environmentally relevant levels) can stimulate cancer cell proliferation in the fetal testis by interfering with signaling pathways of cellular enzymes and cellular membrane receptors (specifically non-classical estrogen receptors).[676] These authors note that such results not only support the hypothesis of BPA links to TGCC but constitute a nongenomic (i.e., not genotoxic) action of exogenous substances. As noted previously, such carcinogenic action is not included in regulatory evaluations of chemicals for carcinogenicity.

These widely varied results of endocrine disruption, of which only three examples are described above, also illustrate the vast complexity that exists in this field. Moreover, the evidence that mixtures of substances can contribute to effects within the TDS in a cumulative dose-additive manner adds to the sobering implications of allowing exposures to hundreds, and perhaps thousands, of endocrine disrupting substances to continue while scientists and policy makers attempt to understand their implications for the environment and human health.

12.6 Other Cancers

12.6.1 Introduction

Within the large number of cancers where associations exist with environmental exposures, including many noted in Table 5, a research emphasis in this report was placed on the three cancers noted above, that is, breast, prostate and testicular cancer, because of the increasing evidence for links between these cancers and early exposures. This focus was also chosen because of their high prevalence and increasing incidence in the population. Cancers in children and young adults are also noteworthy since the potential for early-life exposures is obviously relevant, given the typically shorter latency period before onset of the disease. As noted in Section 12.1 above, cancers that are most common in children include leukemia, cancers of the brain and nervous system and non-Hodgkin lymphoma. Those most common in young adults also include NHL as well as testicular and thyroid cancers.

Hence, this review is incomplete without noting several additional cancers for which there is also either higher prevalence than other cancers and/or increasing incidence and where there is evidence of links to environmental exposures, particularly where risk appears to arise, or be increased, from early life exposures.

The following discussion briefly describes additional evidence for environmental links to several cancers while recognizing again that multiple risk factors are always involved with any chronic disease, including cancer.

For particulate air pollution, in addition to the extensive evidence of links with both CVD, discussed in Sections 9.2.4 and 9.2.5 above, and respiratory disease, discussed in Section 13.2.3 below, there is extensive epidemiological evidence of associations with lung cancer,[677] among the top three most prevalent cancers in men and women and the leading cause of cancer deaths. While strong evidence links most lung cancers to cigarette smoking, air pollution is also clearly involved.

Radon is also noteworthy with respect to lung cancer. This naturally-occurring gas comes from the natural breakdown of uranium in soil or bedrock.[678] Radon emits alpha particles and other radioactive products. If present in homes it poses a significant lung cancer risk[679] and the National Cancer Institute of Canada estimates that 10% of lung cancer deaths in Canada may be caused by radon exposure.[680] For children, due to lung shape and size differences, as well as faster respiration

676 Bouskine A et al (2009) Low Doses of Bisphenol A Promote Human Seminoma Cell Proliferation by Activating PKA and PKG via a Membrane G-Protein–Coupled Estrogen Receptor. *Environmental Health Perspectives*; 117:1053–1058.

677 Pope CA et al (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Journal of the American Medical Association*; 287:1132–1141.

678 Health Canada, "Healthy Living – Radon" Accessible at www.hc-sc.gc.ca/hl-vs/iyh-vsv/environ/radon-eng.php

679 Krewski D et al (2006) A combined analysis of North American case-control studies of residential radon and lung cancer. *Journal of Toxicology and Environmental Health;* 69(7):533-97.

680 Health Canada and Canadian Mortgage and Housing Corporation (2007) Radon: A Guideline for Canadian Homeowners. www.cmhc-schl.gc.ca/odpub/pdf/61945.pdf

rates, their estimated radiation doses will be higher than for adults. Indeed, the risk of radon-induced lung cancer in children may be almost twice as high as the risk to adults exposed to the same amount of radon.[681]

Two literature reviews, the first on environmental and occupational exposures,[682] and the second on pesticide exposures,[683] report on evidence of links to common cancers. A brief summary of these findings is as follows. For colorectal, bladder and liver cancers, non Hodgkin lymphoma (NHL) and soft tissue sarcoma, there is some evidence of associations with a range of pesticide exposures although it is generally via adult occupational exposure with no particular indication of greater vulnerability related to early life exposures, with the exception of NHL in children and young adults, discussed further below. NHL is additionally associated with occupational exposure to some solvents. Bladder cancer is additionally associated in some studies with chlorination by-products and cadmium, and via occupational exposure to aromatic amines, PAHs and diesel exhaust (where these are co-exposures with tobacco smoke) and via occupational exposure to various solvents. Additionally for soft tissue sarcoma, there is strong causal evidence for exposure to dioxin, ionizing radiation and vinyl chloride and suggestive evidence for associations via exposure to arsenic as well as several pesticides, as noted above.

Evidence for the causal link between prenatal exposure to ionizing radiation and childhood leukemia[684] comes from studies of medical radiation treatment whereas this association is only suspected for children living in proximity to nuclear facilities. For example, a meta-analysis[685] of European studies into this association, (a majority of which found elevated though not usually statistically significant rates of leukemia), showed an increase in childhood leukemia near nuclear facilities, but did not support a hypothesis to explain the excess.

Other environmental risk factors associated with childhood leukemia include maternal occupational exposure to pesticides during pregnancy. A meta-analysis[686] found a more than 2-fold increase in the risk of leukemia in all studies combined in contrast to studies of father's occupational exposure to pesticides where the association with leukemia was weaker and less consistent. A second systematic review[687] found childhood leukemia positively associated with residential pesticide exposures. A third literature review[688] of studies published between 1992 and 2003 of associations between pesticides and cancer found that most studies on NHL[689] [690] and leukemia[691] showed positive associations, particularly via maternal occupational exposure. Many studies showed positive associations between pesticide exposure and solid tumours with the most consistent associations found for brain[692] [693] and prostate cancer. An association was also found between kidney cancer in children and high and prolonged parental occupational pesticide exposure. These authors conclude that their findings support attempts to reduce exposure to pesticides around the home (non-commercial use of pesticides) and on the job.

681 Agency for Toxic Substances and Disease Registry, Case Studies in Environmental Medicine (2010) Radon Toxicity: Who is at Risk. www.atsdr.cdc.gov/csem/radon/whosat_risk.html

682 Clapp RW et al (2007) *Environmental and Occupational Causes of Cancer, New Evidence 2005-2007*. Prepared for the Cancer Working Group of the Collaborative on Health and the Environment by the Lowell Center for Sustainable Production, University of Massachusetts at Lowell.

683 Lyons G and Watterson A (2010) *A Review of the Role Pesticides Play in Some Cancers: Children, Farmers and Pesticide Users at Risk?* Prepared for CHEM (Chemicals, Health and Environment Monitoring) Trust.

684 Doll R and Wakeford R (1997) Risk of childhood cancer from fetal irradiation. *British Journal of Radiology*; 70(830):130-139.

685 Baker PJ and Hoel D. Meta-analysis of standardized incidence and mortality rates of childhood leukaemia in proximity to nuclear facilities. *European Journal of Cancer Care*; 16(4):355-363.

686 Wigle DT et al (2009) A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure, *Environmental Health Perspectives*; 117(10):1505-13.

687 Turner MC et al (2010) Residential pesticides and childhood leukemia: A systematic review and Meta-analysis, *Environmental Health Perspectives*; 118:33-41.

688 Basil KL et al (2007) Cancer health effects of pesticides, systematic review. *Canadian Family Physician*; 53:1704-1711.

689 See also: Infante-Rivard C and Weichenthal S (2007) Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. *Journal of Toxicology and Environmental Health B Critical Reviews;* 10(1-2):81-99.

690 See also: Lyons G and Watterson A (2010) *op. cit.*

691 See also: Lyons G and Watterson A (2010) *op. cit.*

692 See also: Infante-Rivard C and Weichenthal S (2007) *op. cit.*

693 See also: Nielsen SS et al (2010) Childhood Brain Tumors, Residential Insecticide Exposure, and Pesticide Metabolism Genes. *Environmental Health Perspectives*; 118:144–149.

A study[694] of childhood cancer cases in France found associations between maternal prenatal exposure to household pesticides and both leukemia and NHL. Another case-control study[695] of over 500 matched pairs in cancer registries in the U.S. found a significant risk of childhood brain cancer associated with residential use of herbicides with the authors noting their findings as consistent with previous literature. In another case-control study[696] of 550 cases of leukemia (specifically acute lymphocytic leukemia – ALL – the most common form of childhood leukemia) and 100 cases of acute myeloid leukemia (AML) and one or two matched controls per case, paint exposure was identified as a significant risk factor for ALL and solvent exposure was associated with AML.

A population-based case control study[697] in 35 California counties looked at children's exposures to PCBs and several persistent and banned OC pesticides in the home and found that PCBs, which are considered probable human carcinogens, may be an unrecognized risk factor for childhood leukemia. Because PCBs (and persistent pesticides) are known to persist indoors in carpets, samples of house dust were taken. The study found an increased risk of ALL with increasing concentrations of PCBs in dust samples taken in the room in which the child spent the most time.

Thyroid cancer is another cancer for which there is high prevalence and increasing incidence among young adults in Canada. The only environmental exposure linked to thyroid cancer is ionizing radiation, widely accepted as a causal association. This link has been demonstrated in many different situations of medical radiation treatment, in studies of populations exposed to wartime nuclear bombs as well as bomb testing, and in the large increases in thyroid cancer seen several years after the Chernobyl nuclear plant accident among children who lived nearby.[698] [699] [700] The dramatic rise in thyroid cancer in recent decades can be only partly explained by improved diagnosis.[701] Recently available county-specific incidence data for thyroid cancer in the eastern U.S. shows that most of the counties with the highest thyroid cancer incidence are in a contiguous area within a 90-mile radius of 16 nuclear power reactors indicating that radioactive iodine emissions from these plants are a likely etiological factor in these rising rates of thyroid cancer incidence.[702]

Finally, an area of significant controversy is the potential brain cancer risk from prolonged use of cell phones. In the 13-country INTERPHONE study,[703] a very large case–control study of multiple studies of mobile phone use and brain tumours, no increased risk of brain tumours (glioma or meningioma) was observed while results suggested an increased risk of glioma at the highest exposure levels (prolonged use for ten years or more). The investigators state that the possible effects of long-term heavy use of mobile phones require further investigation given their greatly increased use including by children. However, other experts have criticized this study, and the various preceding studies incorporated within it, for methodological problems[704] and misinterpretation of the data, for example by obscuring and understating brain cancer risks among

694 Rudant J et al (2007) Household exposure to pesticides and risk of childhood haematopoietic malignancies: the ESCALE study (SFCE), *Environmental Health Perspectives;* 115:1787-93.

695 Shim Y et al (2009) Parental exposure to pesticides and childhood brain cancer: United States Atlantic Coast Childhood Brain Cancer Study. *Environmental Health Perspectives;* 117(6):1002-6.

696 Scelo G et al (2008) Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. *Environmental Health Perspectives*; 117(1):133-9.

697 Ward M et al (2010) Residential Exposure to Polychlorinated Biphenyls and Organochlorine Pesticides and Risk of Childhood Leukemia. *Environmental Health Perspectives;* 117:1007-13.

698 Wigle D (2003) *Child Health and the Environment*, Chapter 9 Radiation. Oxford University Press.

699 Brown V (2003) Disrupting a Delicate Balance, Environmental Effects on the Thyroid. *Environmental Health Perspectives*; 111(12):A642-A649.

700 Reiners C et al (2008) Thyroid cancer in infants and adolescents after Chernobyl. *Lancet*; 371(9612):569-78.

701 Enewold L et al (2009) Rising Thyroid Cancer Incidence in the United States by Demographic and Tumor Characteristics, 1980-2005. *Cancer Epidemiology, Biomarkers and Prevention*; 18(3):784-791.

702 Mangano JJ (2009) Geographic Variation in U.S. Thyroid Cancer Incidence and a Cluster Near Nuclear Reactors in New Jersey, New York, and Pennsylvania. *International Journal of Health Services*; 39(4):643–661.

703 The INTERPHONE Study Group (2010) Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study. *International Journal of Epidemiology*; 39(3):675–694.

704 Hardell L et al (2008) Methodological Aspects of Epidemiological Studies on the Use of Mobile Phones and Their Association with Brain Tumours. *The Open Environmental Journal*; 2:54-61.

the heaviest cell phone users. Concerns have also been raised about industry funding sources, among other criticisms.[705,706,707]

The controversy around the INTERPHONE study somewhat belies its original intended purpose, that is, to attempt to resolve the fact that several previous studies indicated associations between heavy cell phone use and brain tumours while others did not. Where agreement exists among these various competing views is that scientists know almost nothing about potential adverse effects of cell phone use, particularly prolonged cell phone use, on children, although there is reason to expect greater vulnerability, for example due to their developing brains and relatively thinner bones in their skulls allowing greater penetration of electromagnetic fields. Notably, the International Agency for Research on Cancer (IARC) convened experts to assess this cancer hazard. In May of 2011, this review resulted in an IARC classification of radiofrequency electromagnetic fields as possibly carcinogenic to humans (IARC Group 2B) based on the increased risk for glioma associated with wireless phone use.[708]

The above discussion briefly reviews evidence for associations with environmental exposures among several cancers that are at high prevalence and/or increasing incidence in Canada. Unlike the preceding and more comprehensive discussion of risk factors for breast, prostate and testicular cancer, the above discussion omits a review of other risk factors. To summarize in very broad terms, it is reasonable to note that the well-established risk factors for cancer discussed elsewhere in this report are equally relevant to the cancers discussed in this section and so include overweight and obesity (and associated biochemical conditions), sedentary lifestyles, poor nutrition and smoking. Notably, there is evidence that chronic stress is also a risk factor for accelerating cancer,[709] as is the case with risk factors for CVD, discussed in Section 9.2, above. In addition, alongside the cancer risk of obesity and associated biochemical conditions,[710,711,712] diabetes is a risk factor for several cancers,[713] including NHL.[714]

12.7 Early Exposures and Cancer – Key Points

- Cancer represents a considerable chronic disease burden in Canada, having overtaken CVD as the leading cause of death.
- While cancer mortality is declining overall, it is predicted that one in four Canadians will die from cancer.
- The most common cancers in Canada vary by sex and are breast, prostate, lung and colorectal cancers.
- Cancer agencies in Canada note increasing trends in certain cancers (e.g. thyroid) and distinct trends among adolescents and young adults, although cancer is largely still a disease of older adults.
- Although influential work from the 1980s minimized the role of environmental factors in cancer causation, more recent research is seeking to correct that now outdated view.
- Genetic inheritance accounts for a small percent of cancers. Genetic polymorphisms may interact with environmental factors to influence cancer causation in people. Additional processes affecting cancer susceptibility, such as cellular detoxification can be influenced by exogenous variables such as stress and nutrition, which are in turn affected by the

705 Morgan LL et al (2009) Cellphones and Brain Tumors 15 Reasons for Concern. Science, Spin and the Truth Behind INTERPHONE. Unpublished study.
706 Morgan LL et al (undated) Re-evaluation of the INTERPHONE Study - Application of a correction factor. Unpublished study.
707 Davis DL (2010) *Disconnect - The Truth About Cell Phone Radiation, What the Industry Has Done to Hide It, and How to Protect Your Family*. Dutton, New York.
708 International Agency for Research on Cancer (2011) IARC Classifies Radiofrequency Electromagnetic Fields as Possibly Carcinogenic to Humans. Press Release No. 208. 31, May 2011.
709 Sloan EK et al (2010) The Sympathetic Nervous System Induces a Metastatic Switch in Primary Breast Cancer. *Cancer Research*; 70(18); 7042–52.
710 Gnagnarella P et al (2008) Glycemic index, glycemic load, and cancer risk: a meta-analysis. *American Journal of Clinical Nutrition*; 87:1793– 801.
711 Larsson SC and Wolk A (2007) Obesity and risk of non-Hodgkin's lymphoma: A meta-analysis. *International Journal of Cancer;* 121:1564–1570.
712 Renehan AG et al (2008) Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet;* 371(9612):536-7.
713 Giovannucci E et al (2010) Diabetes and Cancer, American Diabetes Association Consensus Report. *Diabetes Care*; 33:1674–1685.
714 Mitri J et al (2008) Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Diabetes Care*; 31(12):2391-2397.

broad SDOH.

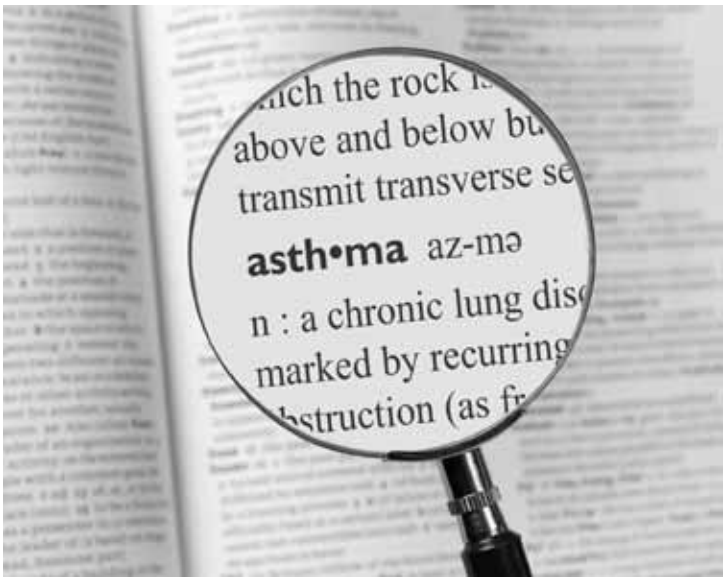
- There are many cancer risk factors, including the well known behavioural risk factors (smoking, diet, physical activity) along with others such as alcohol consumption, obesity, and social factors.
- A very large and growing body of evidence points also to multiple environmental and/or occupational exposures as contributors to many different cancers, including those in highest prevalence.
- Adding to the well understood somatic mutation theories of cancer causation is expanding knowledge of the epigenetic mechanisms and events which are seen as central to understanding how cancers develop and progress from the influence of external factors, including environmental contaminants. Furthermore, this knowledge indicates that epigenetic mechanisms are also centrally involved in early life events that can lead to later life cancer.
- Molecular epidemiology offers promise as an approach to detecting and preventing cancer development by identifying biomarkers, including those that result from early life exposures.
- A wide range of chemical substances and physical agents are implicated in human carcinogenicity with most information known from studying adults exposed occupationally or environmentally.
- The evidence for greater vulnerability of prenatal or childhood exposure to known or suspected carcinogens suggests two overall mechanisms: direct but delayed causation and increased sensitivity to later exposures.
- This section focuses on the early life exposure risk factors related to three cancers of concern because of their high prevalence, breast, prostate and testicular cancers.
- For early life exposures and breast cancer, the greatest risks appear to come from large categories of substances suspected of endocrine disruption, either as xenoestrogens (i.e., foreign estrogens) or via other endocrine disrupting properties, including dioxins, PCBs, and most of the persistent OC pesticides such as DDT, its metabolite DDE, as well as dieldrin, aldrin, heptachlor and chlordane. Other xenoestrogenic substances, like BPA, are implicated as increasing breast cancer risks via xenoestrogenic mechanisms, on the basis of animal studies. More limited evidence exists for links to breast cancer from exposure to alkylphenols, several metals, phthalates, parabens, UV filter components of sunscreens and the food additives bovine somatotropin (rBST) and zeranol.
- Experts describe the potential for these substances to exert permanent epigenetic changes (during mammary gland development *in utero*) that alter later susceptibility, often before and during puberty, to other factors that can initiate breast cancer.
- Based on occupational studies, some evidence for increased risks of prostate cancer, possibly from endocrine disruption mechanisms, implicates some pesticides, PCBs and cadmium.
- Evidence highlighting early life exposure links to later prostate cancer is seen from endocrine-disrupting modes of action from the synthetic hormone DES and BPA.
- Epidemiological and toxicological evidence supports the hypothesis that disruptions in sex hormones, occurring during fetal development, play a role in the current increasing incidence of testicular cancer and of genital abnormalities in boys.
- Experts have identified a broader range of risk factors, including environmental exposures, as being involved in the etiology of the developmental disorder called Testicular Dysgenesis Syndrome (TDS) which they postulate is an indicator also of testicular cancer risk.
- The TDS concept is a unifying hypothesis that invokes a common fetal origin of four effects on the male reproductive system, including the birth defects cryptorchidism (undescended testicles) and hypospadias, poor semen quality and the later development of testicular cancer. Multiple animal studies have demonstrated these effects from

endocrine disrupting chemicals.

- Some pesticides, certain phthalates, perfluorochemicals and bisphenol A may all disrupt fetal testes development and are implicated in the development of TDS.

13.0 Respiratory Disease – Focus on Asthma

13.1 Prevalence of Respiratory Diseases in Canada



The Public Health Agency of Canada states that respiratory diseases affect over 3.5 million people in Canada, (as summarized in Table 2 in Section 2 above). This number tallies available data for asthma, chronic obstructive pulmonary disease (COPD), lung cancer, tuberculosis (TB), and cystic fibrosis. With data unavailable for several other respiratory diseases, including influenza, pneumonia and other conditions, PHAC also states that the number of people affected by respiratory disease is likely much higher. The two most prevalent respiratory diseases, by a large margin, are asthma and COPD (annual estimate of 2.74 million and over 754,000 physician-diagnosed cases, respectively), followed by lung cancer (over 20,500 cases).[715] Hence, asthma comprises a very large proportion of total respiratory disease in Canada.

The above numbers are provided for the sake of overall context. However, the balance of this review of respiratory disease focuses on asthma as a highly prevalent respiratory disease where there is evidence of associations with early environmental exposures in conjunction with a complex range of additional risk factors. As well, the decision to focus on asthma in this review is further based upon the fact that although air pollution is implicated in worsening of COPD symptoms[716,717,718] and may increase the risk of lung cancer,[719] it is well-established in the scientific literature that cigarette smoking and exposure to ETS, or second hand smoke, are the most significant of risk factors for both, described as the principal underlying cause of 80 to 90% of all cases of COPD[720] and lung cancer.[721] However, it should also be noted that while active smoking is recognized as the main cause of COPD, adults with asthma are at increased risk of developing COPD.[722]

715 Public Health Agency of Canada (2007) Life and Breath: Respiratory Disease in Canada. Available at http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/pdf/PHAC-Respiratory-WEB-eng.pdf

716 Desqueyroux H et al (2002) Effects of air pollution on adults with chronic obstructive pulmonary disease. *Archives of Environmental Health;* 57(6):554-60.

717 Schikowski T et al. (2005). Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respiratory Research;* 6(1):152.

718 Osman LM et al. (2007) Indoor Air Quality in Homes of Patients with Chronic Obstructive Pulmonary Disease, *American Journal of Respiratory and Critical Care Medicine;* 176:465–472.

719 Pope CA et al (2002) Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *Journal of the American Medical Association*; 287:1132-1141..

720 Canadian Thoracic Society (2010) *The Human and Economic Burden of COPD: A Leading Cause of Hospital Admission in Canada*. February, 2010.

721 Cancer Care Ontario (2009) Ontario Cancer Facts: Impact of smoking on cancer mortality trends in Ontario (Jan. 2009). http://www.cancercare.on.ca/cms/one.aspx?pageId=35172

722 Burrows B et al, 1988. A re-examination of risk factors for ventilary impairment. *American Review of Respiratory Disease;* 138:829-836.

13.1.1 *Prevalence of Asthma*

In addition to being at such high prevalence compared to other respiratory diseases, asthma is the most common chronic illness in children. Prevalence numbers vary depending on whether asthma is self-reported or physician-diagnosed with overall numbers for the former being typically higher. According to data collected in the National Longitudinal Survey of Children and Youth, physician-diagnosed asthma affected 11 per cent of children in Canada aged 0 to 11 years in 1994-1995, and this number rose to 13 per cent of children, in the same age range, in 2000-2001.[723] More recent data indicate improvements. Among children aged 2 to 7 years, 9.8 per cent were diagnosed with asthma in 2008-09, down from 13.2 per cent in 2001-01.[724] Despite this change, the levels of asthma have roughly quadrupled since the early 1980s when the prevalence of self-reported asthma in those aged 0 to 19 was just over two percent.[725]

The Public Health Agency of Canada[726] notes that since 1994-95, physician-diagnosed asthma prevalence has been consistently higher among boys than girls though the reverse is true among adults. This tendency has been observed in large cohort studies[727,728] and may be explained by the fact that boys have smaller lung size at birth but larger in adulthood.[729] At puberty, the situation reverses with asthma incidence and severity increasing among girls compared to boys.[730] Some children grow out of the disease, but for many it is a lifelong condition. Asthma prevalence among adults is also on the rise with higher prevalence among women. Data for the 10-year period between 1994-5 and 2005 indicate an increase of 60 percent among women in the 35-44 year age group and 80% among women age 45-64 years. Prevalence increased 41 percent among men in the 35 to 44 age group.[731]

An additional sub-set of people that appear to be disproportionately affected by asthma are those diagnosed with chemical hypersensitivity. In a random population survey of over 1000 Americans in four seasonal cohorts, 12.9% of the sample reported asthma. Almost two thirds reported that it had begun in childhood or adolescence. Chemical hypersensitivity was reported by 11.6% of the overall sample, but by 31.4% of those with asthma. Similar percentages of chemical hypersensitivity were found in the childhood (<11 years of age) and adult (>20 years) asthma onset groups (25.8% and 29.6% respectively), but a much higher percentage (52.4%) of those with adolescent onset asthma (age 11 to 20 years) reported sensitivity to chemicals.[732]

There is widespread consensus that the rapid rise in asthma prevalence worldwide, including in Canada, over the last four decades is real, not an artifact of better diagnosis. Since several generations would be necessary for genetic factors alone to be responsible for the increase, understanding the role of environmental factors is critically important.

13.2 Asthma Risk Factors

Asthma is a complex disease with multiple risk factors. They include those that are known or suspected in the development of asthma as well as those that are known or suspected as triggers of asthma episodes among people who already have the disease.

723 Statistics Canada. Garner R and Kohen D. (2008) Changes in the prevalence of asthma among Canadian children Available at http://www.statcan.gc.ca/pub/82-003-x/2008002/article/10551-eng.pdf

724 Thomas EM (2010) Recent trends in upper respiratory infections, ear infections and asthma among young Canadian children. *Health Reports*; 21(4); 1-6. Statistics Canada Catologue No. 82-003-X

725 Health Canada (1999) Population and Public Health Branch. Measuring Up – A Health Surveillance Update on Canadian Children and Youth: Asthma Prevalence.

726 Public Health Agency of Canada (2007) *Life and Breath*, *op. cit.*

727 Clough JB (1993) The Effect of Gender on the Prevalence of Atopy and Asthma. *Clinical and Experimental Allergy*; 23: 883–885.

728 Martinez FD et al (1995) Asthma and Wheezing in the First Six Years of Life. *New England Journal of Medicine*; 332(3):133-138.

729 Tepper RS et al (1986) Physiological growth and development of the lung during the first year of life. *American Review of Respiratory Diseases*; 134:5139.

730 Becklake MR et al (1999) Gender differences in airway behaviour over the human life span. *Thorax*; 54(12):1119-1138.

731 Public Health Agency of Canada (2007) *Life and Breath*, op. cit.

732 Caress SM and Steinemann AC (2009). Asthma and chemical hypersensitivity: prevalence, etiology, and age of onset. *Toxicology and Industrial Health;* 25:71-78.

An extensive review[733] of the literature on asthma risk factors notes that many longitudinal studies indicate that childhood asthma susceptibility likely originates during prenatal and early postnatal development. It discusses the multiple risk factors for asthma onset in three overall categories: host, genetic and environment as well as the multiple interactions therein. With minor adaptation, the balance of this section follows the same approach and reviews these three categories of risk factors as follows:

- *host* (e.g., immunity and lung function)
- *genetic* (e.g., the diverse asthma phenotypes, gene-environment interactions, gene-gene interactions and epigenetics)
- *environment* (e.g., pollution sources, nutrition and gut colonization, respiratory infections, and psychosocial environment and stress).

The following discussion also places greater emphasis on the evidence about early environmental exposures and asthma, in particular where these interact with genetic or host risk factors.

13.2.1 Host Risk Factors

Among the individual or host risk factors for asthma are key aspects of how the immune system and lungs develop.

The immune system develops throughout the body in most organs and tissues and this development extends across the entire period of gestation from at least week six of pregnancy and into early childhood. In a literature review[734] about gene-environment interactions in asthma that also seeks an explanation for rising asthma prevalence, the authors note the insufficient time available for genetic changes to account for the increase but also point to considerable evidence underscoring the improbability of it being attributable to changes in environmental allergens, as these occur in modern domestic settings. They note instead evidence for the likelihood of interactions between genetic and environmental factors in infants and young children resulting in an altered immune response that predisposes to asthma onset.

In a review[735] discussing perinatal immunotoxicity issues, the authors note seven discrete stages of prenatal or postnatal immune system development, many of which have to do with related development of a healthy respiratory system. For example, during lung development, animal studies show that key aspects of immune system development (specifically, the alveolar macrophages) are part of perinatal and postnatal lung development. The authors note that sensitivity of the perinatal lung to environmental exposures is tied to alterations in these same aspects of immune system development, influencing regulatory and host defence mechanisms in the lung.

The various stages of immune system development also include key transitions that must occur at birth. In the womb, the immune system T cells of the fetal-maternal unit must be compatible to avoid pregnancy complications. After birth, the infant immune system must shift to create an independent immune system. This change must occur rapidly after birth and appears to continue until about age six months while the child's immune system maturation continues until at least age two. Longitudinal studies that have elucidated the early life immune system response in future asthmatics suggest gene-environment interactions in infants and young children that create a response in the immune system T cells (specifically, the dominance of the T_H2 phenotype) that predisposes for asthma onset.[736]

Despite many decades of extensive research, experts do not fully understand what causes asthma though it is clearly understood to manifest as an immunological response to aeroallergens,

733 Subbarao P et al (2009) Epidemiology of asthma: risk factors for development. *Expert Review of Clinical Immunology*; 5(1):77-95.
734 Patiño CM, Martinez FD (2001) Interactions between genes and environment in the development of asthma. *Allergy;* 56:279-286.
735 Dietert RR and Piepenbrink MS (2006) Perinatal Immunotoxicity: Why Adult Exposure Assessment Fails to Predict Risk. *Environmental Health Perspectives;* 114(4):477-83.
736 Dietert RR and Piepenbrook MS (2008) Early life and immune balance: protecting the womb to delay the tomb. *Human and Experimental Toxicology;* 27:129-34.

in particular as inflammation of the airways of the lungs. Lung development begins in early pregnancy and extends to about age 18 with many varied developmental stages and differing vulnerabilities across each. Exposure to environmental risk factors, including toxic substances, *in utero* and inhaled after birth, across this long timeframe have the potential to influence overall growth and function of the respiratory system and thus contribute to chronic lung disease.[737] The different vulnerabilities to toxic substances during the many developmental stages of a child's lungs are a function of immaturity and ongoing development but also child-adult differences that contribute to unique and often larger exposures in children. For example, children tend to be more active and they breathe faster than adults, they breathe more air proportional to their size than adults and they breathe lower to the ground where certain contaminants tend to be more concentrated. They also tend to do more mouth-breathing reducing the filtering function that occurs with nose-breathing.[738]

A recent review[739] of the literature on developmental lung biology and toxicology, mechanistic studies, and supporting epidemiology looks at studies of the nutritional and endogenous chemical environment affecting lung development and altered adult lung function. The authors point to the expanding literature on the DOHaD concept (discussed in Section 8.1 above) noting extensive epidemiological evidence of associations between low birth weight, under-nutrition and other factors linked to later life respiratory disease including multiple studies demonstrating that lung function in both asthmatics and non-asthmatics is set by early life events and that lung function in infancy predicts pulmonary function throughout life. Building upon this evidence they further note that *in utero* and early post-natal chemical exposures influence lung structure and function in children and adults and may predispose to COPD and other respiratory disorders (as discussed further in Section 13.2.3.7 below). Potential mechanisms include interference with factors in developmental processes that are highly conserved across species such as gene regulation, molecular signaling, and growth factors involved in branching morphogenesis and alveolarization.

13.2.2 Genetic Risk Factors

A great deal of literature[740] reviews the role of genetic factors in causing asthma and it is not reviewed in detail here other than to note that these many investigations reveal a highly complex situation of numerous genes, (governing multiple aspects of the immune and respiratory systems), and extensive heterogeneity that also varies by gender and age, including the suggestion that adult onset asthma should even be considered a different disease from childhood onset asthma.[741]

Added to the complexity of asthma genetics and the heterogeneity across asthmatic individuals is the fact that asthma onset involves multiple gene-environment interactions, gene-gene interactions, resulting variability in immune and respiratory system development, all of which can affect whether and how asthma occurs in genetically predisposed individuals. With continued investigation comes recognition of the need to sort out the interplay between genetic variants, developmental processes and epigenetic mechanisms. This conclusion arises from the fact that robust epidemiological evidence points to developmental processes during early life, including in the womb, as critical windows of vulnerability affecting whether genetically susceptible individuals develop asthma or allergies with additional strong evidence pointing to epigenetic mechanisms playing a central role.[742]

At least two windows of vulnerability for epigenetic changes are apparent. These include possible environmentally-induced changes *in utero* affecting how fetal genes are expressed, thus influencing later allergy and asthma risk. Then in early life, further epigenetic changes may occur if environmental factors modify a child's genome potentially causing and/or prolonging allergy

737 Soto-Martinez M and Sly PD (2010) Relationship between environmental exposures in children and adult lung disease: The case for outdoor exposures. *Chronic Respiratory Disease, Review Series: what goes around, comes around: childhood influences on later lung health*; 7(3):173-186.
738 Bateson TF and Schwartz J (2008) Children's response to air pollutants. *Journal of Toxicology and Environmental Health* A; 71:238–243.
739 Miller MD and Marty MA (2010) Impact of Environmental Chemicals on Lung Development. *Environmental Health Perspectives*; 118:1155–1164.
740 Ober C and Hoffjan S (2006) Asthma genetics 2006: the long and winding road to gene discovery. *Genes and Immunity*; 7(2):95-100.
741 Martinez FD (2007) Gene-Environment Interactions in Asthma. With Apologies to William of Ockham. *Proceedings of the American Thoracic Society*; 4(1):26-31.
742 Vercelli D (2008) Discovering susceptibility genes for asthma and allergy. *Nature Reviews – Immunology*; 8(3):169-182.

or asthma. For example, some experts[743] describe the inappropriate retention of fetal genes expressing T_H2 immune cells as the hallmark of early asthma. They are supported in this view by others[744] who propose that epigenetic changes induced by environmental factors are the reason for allergies and asthma being associated with the continued and inappropriate retention of fetal genes expressing T_H2 genes that were not silenced during late pregnancy or early infancy.

Preliminary results from a study[745] of a sub-cohort within the Columbia University Center for Children's Environmental Health longitudinal cohort study appear to support this view. As noted above, with respect to the apparent link to immune system dysfunction in the risk of asthma onset, these researchers point to the fact that multiple epidemiological studies suggest prenatal and/or early life exposure to pollutants and allergens modify later life lung function and manifest in the T helper cell allergic phenotype.[746] They hypothesize that epigenetic marks (specifically DNA methylation) associated with transplacental PAH exposure and/or childhood asthma risk could be found in fetal tissues. Preliminary results indicate that methylation of a particular gene sequence was significantly associated with maternal airborne PAH exposure and with parental report of asthma symptoms in children prior to age five. If these results are validated, they may have discovered a biomarker for transplacental PAH exposure and/or a biomarker for environmentally-related asthma. The authors note that these results provide a relatively simple means of distinguishing children born to mothers with high airborne PAH exposure from those who were not. More broadly, this study points the way to potential means of discerning other epigenetic biomarkers that could be useful within exposure and toxicity assessments of environmental contaminants. It also provides support for the emerging theory of early origins of later life disease development.

Thus, environmental factors modifying the epigenome in early life appear to play a crucial role in the susceptibility to asthma development. Experts note that increased understanding of these epigenetic mechanisms adds to the well-established understanding that asthma results from, albeit complex, gene-environment interactions, and moreover, holds promise for discovering how to reverse a theoretically preventable environmental disease.[747]

13.2.3 Environmental Risk Factors

A wide variety of environmental risk factors exist for asthma. They include:

- cigarette smoking and ETS;
- allergens (dust mites, pet dander, pollen, moulds, etc.);
- childhood viral infections, potentially causing allergen sensitization;
- nutritional factors and gut colonization, prenatally and in childhood that influence immune system development;
- the psychosocial environment and stress; and
- indoor and outdoor air pollution. [748,749,750,751,752]

Evidence for associations between environmental risk factors and asthma is often inconsistent and it is routinely made more complex by the apparent influence of gene-environment interactions. The focus of the discussion that follows is on environmental risk factors related to

743 Anderson GP (2002) The immunobiology of early asthma. *Medical Journal of Australia*; 177 (6 Suppl): S47–S49.
744 Bousquest J et al (2004) Epigenetic inheritance of fetal genes in allergic asthma. *Allergy;* 59:138–47.
745 Perera F et al (2009) Relation of DNA Methylation of 59-CpG Island of ACSL3 to Transplacental Exposure to Airborne Polycyclic Aromatic Hydrocarbons and Childhood Asthma. *PLoS ONE*; 4(4):e4488
746 Miller RL and S Ho (2008) Environmental Epigenetics and Asthma - Current Concepts and Call for Studies. *American Journal of Respiratory and Critical Care Medicine*; 177:567-573.
747 Miller RL and S Ho (2008) Environmental Epigenetics and Asthma. *American Journal of Respiratory and Critical Care Medicine*; 177:567-573.
748 Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma, Updated 2009. www.ginasthma.org
749 Friedlander SL et al (2005) Viral infections, cytokine dysregulation and the origin of childhood asthma and allergic diseases. *Pediatric Infectious Diseases Journal*; 24(*Suppl.* 11):S170-S176.
750 Penders J et al (2007) The role of the intestinal microbiota in the development of atopic disorders. *Allergy*; 62(11):1223-1236.
751 Dietert RR (2008) Developmental Immunotoxicity: Focus on Health Risks. *Chemical Research and Toxicology;* 22:17-23.
752 Wright RJ et al (2005) The impact of stress on the development and expression of atopy. *Current Opinions in Allergy and Clinical Immunology*; 5(1):23-29.

pollution or chemical exposures. First however, other environmental risk factors are noted and/or very briefly discussed.

13.2.3.1 *Cigarette Smoking and Environmental Tobacco Smoke*

A vast amount of literature, not summarized here, documents the many health concerns and links to asthma related to cigarette smoking and ETS. These exposure risks are of significant concern both prenatally and during childhood.[753,754]

13.2.3.2 *Allergens from Natural Sources*

Similarly, considerable evidence exists on the links between asthma and allergens of natural origins such as dust mites, pet dander, etc. and nor is it summarized here except to note that airborne allergens and pollutants tend to be most often associated with the worsening of asthma symptoms. Whether they are causal factors in asthma onset is often uncertain although dust mites are considered causal factors in both onset and as asthma triggers.[755]

13.2.3.3 *Childhood Lower Respiratory Tract Infections*

For childhood viral infections in the lower respiratory tract, conflicting evidence points to both protective and pathogenic effects in children and it appears, not surprisingly, that the response is modulated by gene-environment interactions.[756]

13.2.3.4 *Nutrition, Gut Colonization and Obesity*

With respect to nutritional issues as environmental risk factors, it is noteworthy that an unhealthy diet, low in antioxidants and essential fatty acids,[757] as well as the choice not to breastfeed,[758] are associated with asthma onset, although the relationship with breastfeeding is unclear and controversial.[759] These relationships appear to be the result of healthy foods, likely including breast milk, assisting with the development of a healthy immune system and related allergy resistance, including via gut colonization. In contrast, multiple cross-sectional and case-control studies show an association between greater prevalence of asthma and obesity[760] in children and adults, more so among women, although it remains unclear whether underlying asthma, and the tendency towards related inactivity, causes obesity or whether obesity can cause asthma.[761] The latter seems unlikely however as weight loss among asthma patients tends to improve lung function.[762]

13.2.3.5 *Socio-Economic Status and Stress*

As discussed throughout this report socio-economic status influences lifelong health and lower socio-economic status is associated with greater asthma prevalence though, again, some studies report conflicting results. As well, numerous studies[763] link stress, a common aspect of living in poverty, to both asthma onset and as an asthma trigger, including a study in British Columbia showing interactive effects between stress, traffic-related air pollution and asthma.[764] Laboratory

753 Lux A et al (2000) Wheeze associated with prenatal tobacco smoke exposure: a prospective, longitudinal study. *Archives of Disease in Childhood*; 83(4):307-312.

754 Chilmonczyk BA et al (1993) Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. *New England Journal of Medicine*; 328(23):1665-9.

755 Institute of Medicine (2000) Committee on the Assessment of Asthma and Indoor Air, Division of Health Promotion and Disease Prevention, *Clearing the Air: Asthma and Indoor Air Exposures*.

756 Lemanske RF et al (2006) Asthma: factors underlying inception, exacerbation, and disease progression. *Journal of Allergy and Clinical Immunology;* 117(2 Suppl. Mini-Primer):S456-S461.

757 Devereux G et al (2005) Diet as a risk factor for atopy and asthma, *Journal of Allergy and Clinical Immunology;* 115:1109-17.

758 Friedman NJ and Zeiger RS (2005) The role of breast-feeding in the development of allergies and asthma, *Journal of Allergy and Clinical Immunology;* 115:1238-48.

759 Duncan JM and Sears MR (2008) Breastfeeding and allergies: time for a change in paradigm? *Current Opinions in Allergy and Clinical Immunology;* 8(5):398-405.

760 Beuther DA et al (2006) Obesity and asthma. *American Journal of Critical Care and Respiratory Medicine;* 174(2):112-19.

761 As reviewed in Subbarao, 2009, *op cit*.

762 Schaub B et al (2005) Obesity and asthma, what are the links? *Current Opinions in Allergy and Clinical Immunology*; 5(2):185-193.

763 Wright et al 2005, *op. cit.* and as reviewed in Subbarao, 2009, *op cit*.

764 Chen E et al (2008) Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environmental Health Perspectives*; 116:970-975.

studies of rats also show a relationship between stress and greater susceptibility to adverse effects of air pollution.[765]

A link to the combined effect of stress and air pollution is also apparent in a recent study[766] of a large cohort of children in Southern California. Researchers followed nearly 2500 children for three years with no history of respiratory problems. They also measured parental stress and parental education, as an indicator of socio-economic status, as well as traffic-related air pollution exposure. Those children who developed asthma by kindergarten or first grade had parents with stressful lives and also lived near high levels of traffic-related pollution. Parental stress alone did not increase asthma risk, whereas risk of asthma was apparent for air-pollution exposure and this risk increased when combined with high parental stress levels.

13.2.3.6 Indoor and Outdoor Air Pollution and Asthma

For environmental exposures resulting from pollution and other human activities or from consumer products, evidence of associations exist between asthma (onset and asthma triggers) and the following wide range exposures:[767,768,769,770]

- the Criteria Air Contaminants:
  - Ozone (O_3);
  - Carbon monoxide (CO);
  - Respirable particulate matter (PM_{10} and $PM_{2.5}$ where the subscript denotes particle diameter in microns);
  - Nitrogen dioxide (NO_2);
  - Sulphur dioxide (SO_2);
  - Many different VOCs.
- Hazardous Air Pollutants:
  - including numerous polycyclic aromatic hydrocarbons (PAHs) (such as benzene and 1,3-butadiene), aldehydes (e.g., formaldehyde, acetaldehyde) acid vapours and aerosols, diesel exhaust.
- Indoor Air Pollutants (with some overlap with the above two categories):
  - Nitrogen dioxide (NO_2);
  - Formaldehyde and other hazardous air pollutants, VOCs or phthalates contaminating the indoor environment from outdoor sources or arising from consumer products, particularly cleaning, laundry and personal care products containing fragrances, especially aerosol sprays.[771] Fragrances are composed of many proprietary VOCs,[772] and are well-known asthma triggers,[773] prompting U.S. action on fragrance-free workplaces[774] and safer product labelling.[775]

765 Clougherty JE (2010) Chronic Social Stress and Susceptibility to Concentrated Ambient Fine Particles in Rats. *Environmental Health Perspectives*; 118:769–775.

766 Shankardass K et al (2009) Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proceedings of the National Academy of Sciences;* 106(30):12406-12411.

767 Gilliland FD and R McConnell (2004) Effects of Air Pollution on Lung Function Development and Asthma Occurrence. Chapter 24 in Harding R et al (eds) *The Lung: Development, Aging and the Environment*, Elsevier Academic Press.

768 Leikaf, GD (2002) Hazardous Air Pollutants and Asthma. *Environmental Health Perspectives;* 110 (*Suppl*. 4):505-526.

769 Mendell MJ (2007) Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: a review. *Indoor Air;* 17:259-277.

770 Pandya RJ et al (2002) Diesel Exhaust and Asthma: Hypotheses and Molecular Mechanisms of Action. *Environmental Health Perspectives;* 110 (*Suppl* 1): 103-112.

771 Nazaroff WW and Weschler CJ (2004) Cleaning products and air fresheners: exposure to primary and secondary air pollutants. *Atmospheric Environment*; 38(18):2841-2865.

772 Steinemann AC (2009) Fragranced consumer products and undisclosed ingredients. *Environmental Impact Assessment Review*; 29:32-38.

773 Elberling J et al (2007) Increased release of histamine in patients with respiratory symptoms related to perfume. *Clinical and Experimental Allergy*; 37:1676-1680.

774 De Vader CL and Paxson B (2009) Fragrance in the workplace is the new second-hand smoke. *Proceedings of the American Society of Business and Behavioral Sciences*; 16(1):1-11.

775 U.S. Environmental Protection Agency (2011) Design for the environment (DfE) Criteria for fragrances; http://www.epa.gov/dfe/pubs/projects/gfcp/index.htm#GeneralScreen, accessed April 26, 2011.

Taken together, these exposures constitute a complex mixture of substances many of which are synthesized from fossil fuels or are the product of their combustion.

It is worth emphasizing as well that the evidence for harmful effects of fine particulate matter ($PM_{2.5}$) and ozone create significant concern for two important reasons. First, these contaminants are widespread arising from multiple sources, particularly vehicle emissions, and no lower threshold is apparent below which harmful effects cannot be discerned.[776] Second, these two contaminants are in reality complex mixtures, or the result of other complex mixtures of contaminants. Ozone is created by the reaction of nitrogen oxides and VOCs in the presence of sunlight. As well, the surface of particulate matter contains a complex mixture of sulphates, nitrates, ammonium ions, elemental carbon, PAHs, other toxic organic compounds and toxic metals. The smaller the particle, the larger is the surface area that can be covered by these contaminants. Once inhaled, fine ($PM_{2.5}$) and ultrafine ($PM_{1.0}$) particulate matter, and its surface burden of toxic substances, may damage the lung via direct contact and cause the lung to release markers of inflammation into blood circulation. Fine particles can also pass directly into the bloodstream from the pulmonary alveoli, the smallest interior spaces of the lungs.[777]

As noted above, extensive research reported in the scientific literature indicates inconsistent associations between air pollution and asthma onset, with some results suggesting associations but not sufficient to be considered a causal effect[778] while other investigators do consider their results to indicate causal associations.[779,780]

Whether or not the association between air pollution and asthma onset is causal, it is well-established that exposure to outdoor and indoor air pollution can worsen the symptoms of asthma and other respiratory conditions, that is, air pollutants can trigger asthma among already affected individuals. Numerous longitudinal studies conducted in multiple locations around the world demonstrate these associations,[781] for example, the Children's Health Study in Southern California,[782] as echoed in a critical literature review[783] by the Health Effects Institute that concluded there is a causal relationship between traffic-related air pollution and asthma exacerbation.

In a literature review[784] of papers reporting on the results of nine prospective cohorts from six different countries, the authors concluded that traffic exhaust contributes to the development of respiratory illness in childhood and may induce asthma and allergic sensitization. Additional studies continue to lend support to the hypothesis that air pollution directly contributes to asthma onset, such as a recent large population-based nested case-control study in British Columbia.[785]

Another literature review[786] of studies looking at chemicals in residential indoor air as risk factors for respiratory and allergic effects in children noted associations, some strong, with indoor air pollution sources. This evidence most frequently points to formaldehyde, flexible plastics that emit phthalate plasticizers, and new paint as risk factors for respiratory effects. Limited but suggestive evidence also points to risk arising from aromatic and aliphatic chemical compounds as well as risks associated with specific activities or products including renovation and cleaning activities, new furniture, and carpets or textile wallpaper. All of this leads the author to conclude that there

776 Canadian Council of Ministers of the Environment (2007) Canada-Wide Standards for Particulate Matter and Ozone. Appendix A to Guidance Document on Achievement Determination, Canada-Wide Standards for Particulate Matter and Ozone, Revised. http://www.ccme.ca/assets/pdf/1391_gdad_e.pdf

777 Nemmar A et al (2002) Passage of Inhaled Particles Into the Blood Circulation in Humans. *Circulation*;105:411-414.

778 Raaschou-Nielsen O et al (2010) Long term exposure to indoor air pollution and wheezing symptoms in infants, *Indoor Air;* 20:159-167.

779 McConnell R et al (2006) Traffic, Susceptibility, and Childhood Asthma. *Environmental Health Perspectives*; 114:766-772.

780 Parker JD et al (2009) Air Pollution and Childhood Respiratory Allergies in the United States, *Environmental Health Perspectives*; 117:140-47.

781 Eder WE et al (2006) The Asthma Epidemic, *New England Journal of Medicine;* 355(21):2226-35.

782 Peters JM et al (2004) Epidemiologic Investigation to Identify Chronic Effects of Ambient Air Pollutants in Southern California. Prepared for the California Air Resources Board and the California Environmental Protection Agency. http://www.arb.ca.gov/research/abstracts/94-331.htm

783 Health Effects Institute (2010) *Traffic-Related Air Pollution: A Critical Review of the Literature Emissions, Exposure and Health Effects*. HEI Panel on the Health Effects of Traffic-Related Air Pollution, Special Report 17.

784 Bråbäck L and Forsberg B (2009) Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. *Environmental Health*; 8:17-27.

785 Clark NA et al (2010) Effects of Early Life Exposure to Air Pollution on Development of Childhood Asthma. *Environmental Health Perspectives;* 118(2):284-290.

786 Mendell MJ (2007) Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: a review. *Indoor Air;* 17:259-277.

is a need for further research to investigate this "new class of residential risk factors" given their ubiquitous presence in indoor residential environments.

Another international longitudinal study[787] of young adults (mean age was 33) found that common, nonprofessional use of household cleaning products in spray form was associated with new-onset asthma. Investigators consider their findings may have significant public health implications. They note that passive exposure might be relevant for those in the home where sprays are being or have just been applied, noting further a study suggesting a relationship between mother's use of cleaning and other household chemicals during pregnancy, and wheeze in young children.[788] An additional systematic review of studies of associations between formaldehyde exposure and childhood asthma found a significant positive association though the authors note that most studies were cross-sectional.[789]

13.2.3.7 Indoor and Outdoor Air Pollution and Lung Development

Another literature review[790] of environmental factors and developmental outcomes in the lung summarizes extensive evidence of associations between prenatal exposure to ambient air pollution and adverse pregnancy outcomes, as well as associations between postnatal and childhood air pollution exposure and compromised lung development. Specifically, this review, another that preceded it,[791] and additional individual studies,[792] note evidence of associations between air pollution and low birth weight, small for gestational age and preterm birth, all of which can be risk factors for altered respiratory function and chronic respiratory disease.

It bears noting that, in addition to air pollution, any other exposures associated with impacts on intrauterine growth, gestational age or birth weight, are relevant to lung development due to the relationship between these adverse birth outcomes and compromised development of the respiratory system. Another extensive literature review[793] looked at the many complex factors that can contribute to preterm birth, including epidemiological studies concerning environmental exposures. It highlights the fact that potential risk for preterm birth as a result of exposure to environmental pollutants is poorly understood, a reality that includes the common and challenging problem of co-exposures of hundreds or even thousands of chemicals, many with known toxicity, as in cigarette smoke, others with very little information. This review further notes the challenge of assessing cumulative exposures, the impacts of which may be important for preterm birth, but are largely unexplored. In the context of recognizing this data challenge, this review confirms the findings noted above with respect to evidence of associations between preterm birth and air pollution, particularly for sulfur dioxide and particulates and adds to this list, lead and environmental tobacco as risk factors for preterm birth. It further summarizes the evidence, often conflicting, about possible associations with OC and OP pesticides, nitrates in drinking water, arsenic, as well as emerging evidence that raises concerns about phthalates and BFRs. A more recent review summarizes additional evidence about associations between arsenic and impaired fetal growth,[794] while another recent study finds preliminary evidence of associations between polyfluorinated compounds[795] linked to low birth weight and premature births.

A third review[796] of the epidemiological literature investigating air pollution and lung development finds strong support for concluding that air pollution has adverse long-term effects on lung

787 Zock JP et al (2007) The Use of Household Cleaning Sprays and Adult Asthma, *American Journal of Respiratory and Critical Care Medicine*; 176:735–741.

788 Sherriff A et al (205) Frequent use of chemical household products is associated with persistent wheezing in preschool age children. *Thorax*; 60:45–49.

789 McGwin G et al (2010) Formaldehyde Exposure and Asthma in Children: A Systematic Review. *Environmental Health Perspectives;* 118(3):313-17.

790 Kajekar, R (2007) Environmental factors and developmental outcomes in the lung. *Pharmacology and Therapeutics;* 114:129–145

791 Šrám RJ et al (2005) Ambient air pollution and pregnancy outcomes: a review of the literature. *Environmental Health Perspectives;* 113:375-382.

792 Brauer M et al (2008) A Cohort Study of Traffic-Related Air Pollution Impacts on Birth Outcome. *Environmental Health Perspectives;* 116(5):680-686.

793 Behrman RE and Butler AS, eds. (2006) *Preterm Birth: Causes, Consequences, and Prevention.* Report from the Institute of Medicine's Committee on Understanding Premature Birth and Assuring Healthy Outcome. Washington, D.C.: National Academies Press. Chapter Eight: The Role of Environmental Toxicants in Preterm Birth.

794 Vahter M (2008) Health Effects of Early Life Exposure to Arsenic. *Basic & Clinical Pharmacology & Toxicology*; 102:204–211.

795 Stein CR et al (2009) Serum levels of perfluoroctanoic acid and perfluorooctane sulfonate and pregnancy outcome. *American Journal of Epidemiology*; 170(7):837-846.

796 Gotschi T et al (2008) Long-Term Effects of Ambient Air Pollution on Lung Function - A Review. *Epidemiology;* 19(5):690-701.

function growth in children, resulting in deficits of lung function at the end of adolescence. For older children in the California Children's Health Study, the prospective investigation of lung development among those followed from ages 10 to 18, showed associations between air pollution exposure and chronic, adverse effects on lung development.[797]

Across these literature reviews and within the air pollution circumstances investigated in individual studies, researchers find these impacts on lung development and associations with worsening of asthma for both outdoor and indoor air pollutants, but some do not.[798] Many studies note that they are testing these associations given the existence of multiple prior studies showing conflicting results. For example, a longitudinal study[799] of children replicated numerous other findings showing indoor air pollution by nitrogen dioxide was associated with worsening of asthma symptoms, contradicting other studies that did not find this association.

13.2.3.8 Indoor and Outdoor Air Pollution and Effects on the Immune System

Exposures suspected in disrupting various aspects of immune system development include but are not limited to air pollutants (such as ozone and tobacco smoke) and can also include *in utero* exposure to dioxin, PCBs and heavy metals.[800] Evidence about the immunotoxicity of lead is quite extensive. A systematic review of this literature[801] describes animal and human evidence of altered immune system function that may contribute to greater risk of allergies and lowered defenses against infectious agents and cancer. Age-based exposure studies indicate that early life exposures to very low levels of lead (i.e., below the level considered elevated in children), may be associated with later life immune alterations. In exploring the apparent link between lead on the immune system and asthma incidence, more recent research[802] looking at bone marrow cells finds lead associated with an enhanced immune response to allergens. Lead appears to alter the formation and response of dendritic cells that play a role in T cell development; the result is a skewing towards T_H2 cell production at the expense of T_H1.

A systematic review and meta-analysis[803] of phthalates from PVC products indoors indicates a mechanism of phthalate impact on the immune system that could contribute to asthma risk. It also summarizes evidence of associations between phthalate exposure and asthma in child epidemiological studies though noting these studies were limited by inadequate exposure data. In one case control study included in this broader review, the concentration of DEHP (a common phthalate) in indoor dust in Bulgarian homes correlated with allergies, asthma and wheezing in children.[804] Another review[805] of experimental and epidemiological studies echoes this conclusion that mechanisms for allergic sensitization are apparent for several phthalates. As well, epidemiological data indicate a possible correlation between phthalate exposure in indoor air and dust (arising largely from consumer products) and asthma and airway disease in children, though similar limitations remain for exposure data and mechanisms. Another review[806] looks at the evidence of links between asthma and allergies and phthalates, BPA and pesticides. It describes the large number of observational studies demonstrating associations between phthalates and asthma and allergies and a range of animal studies that indicate various mechanisms that may contribute to airway inflammation. For pesticides and BPA, the authors note that fewer studies demonstrate associations, particularly for BPA, but that many studies are suggestive of possible

797 Gauderman WJ et al (2004) The Effects of Air Pollution on Lung Development from 10 to 18 Years of Age. *New England Journal of Medicine;* 351(11):1057-1067.

798 Diette DB et al (2007) Home Indoor Pollutant Exposures among Inner-City Children With and Without Asthma. *Environmental Health Perspectives*; 115:1665-1669.

799 Hansel NN et al (2008) A Longitudinal Study of Indoor Nitrogen Dioxide Levels and Respiratory Symptoms in Inner-City Children with Asthma. *Environmental Health Perspectives;* 116:1428-32.

800 Dietert RR (2008) Developmental Immunotoxicity: Focus on Health Risks. *Chemical Research and Toxicology*; 22:17-23.

801 Dietert RR and MS Piepenbrink (2006) Lead and Immune Function. *Critical Reviews in Toxicology;* 36:359-385.

802 Gao D et al (2007) Lead effects on development and function of bone marrow-derived dendritic cells promotes Th2 immune responses. *Toxicology and Applied Pharmacology;* 222(1):69-79.

803 Jaakkola JJK and Knight TL (2008) The Role of Exposure to Phthalates from Polyvinyl Chloride Products in the Development of Asthma and Allergies: A Systematic Review and Meta-analysis. *Environmental Health Perspectives;* 116:845-853.

804 Kolarik B et al (2008) The association between phthalates in dust and allergic diseases among Bulgarian children. *Environmental Health Perspectives;* 116:98-103.

805 Bornehag CG and Nanberg E (2010) Phthalate exposure and asthma in children. *International Journal of Andrology*,; 33:333-345.

806 Kwak ES et al (2009) Phthalates, Pesticides, and Bisphenol-A Exposure and the Developmental of Non-Occupational Asthma and Allergies: How Valid Are the Links? *Open Allergy Journal*; 2:45-50.

links. For pesticides, the authors describe two studies showing these associations among children. As well, for BPA, they note that animal evidence of *early* exposure is particularly associated with heightened inflammation, including an indication of prenatal and perinatal exposure influencing immune system changes associated with atopy.

For the perfluorinated compounds, perfluorooctanoic acid and perfluorooctane sulfonate (PFOA and PFOS), there is general consensus that these chemicals alter the immune system in experimental animal models.[807] An animal study suggests immuntoxicity of PFOA where exposure appears to augment the IgE response to environmental allergens which can trigger or worsen asthma attacks.[808]

13.3 Early Exposures and Respiratory Disease – Key Points

- Although likely a large underestimate, prevalence of certain physician-diagnosed respiratory diseases in Canada is very high, most prominently asthma (2.74 million), COPD (>754,000), and lung cancer (>20,000).
- The focus in this report is on asthma due to high prevalence, evidence of associations with early environmental exposures (along with complex other risk factors), and because it is the most common chronic illness in children. Doctor-diagnosed asthma affects approximately 10% of Canadian children aged 2-7 years, almost quadruple the prevalence from 20 years earlier.
- Asthma has been found to affect more male children (possibly because of smaller lung size, but less adult males (possibly because of larger lung size). While asthma may improve with puberty, some children are affected lifelong. The prevalence among adult women has been increasing, particularly in early to late middle age (35-64), and in adult men aged 35-44.
- Those with chemical hypersensitivity seem disproportionately affected by asthma, especially that onsets in adolescence (age 11-20).
- There are complex host, genetic, and environmental risk factors for asthma with multiple interactions. Although the cause of asthma has not been fully elucidated, an immunological response to aeroallergens, resulting in inflammation of the lung airways has been noted.
- Environmental factors modifying the epigenome in early life appear to play a crucial role in the susceptibility to asthma development. At least two windows of vulnerability for epigenetic changes are apparent. These include possible environmentally-induced changes *in utero* affecting how fetal genes are expressed, thus influencing later allergy and asthma risk. Then in early life, further epigenetic changes may occur if environmental factors modify a child's genome potentially causing and/or prolonging allergy or asthma.
- Lung development begins in early pregnancy and continues to about age 18. It is vulnerable to developmental interruptions if there is exposure to environmental risk factors *in utero* or inhaled after birth. Greater exposure, compared to adults, occurs in infancy and early childhood for multiple physiological and behavioural reasons.
- Potential mechanisms for how pollutant/chemical exposures can have a lifelong influence on lung structure and function include interference with factors in developmental processes in the lungs and the immune system that are highly conserved across species such as gene regulation, molecular signaling, and growth factors involved in branching morphogenesis and alveolarization. This evidence sits within the DOHaD model including evidence that lifelong lung function in both asthmatics and non-asthmatics is set by early life events such as low birth weight, undernutrition, and other factors.
- There is evidence that interactions between genetic and environmental factors in

807 DeWitt JC et al (2009) Immunotoxicity of Perfluorooctanoic Acid and Perfluorooctane Sulfonate and the Role of Peroxisome Proliferator-Activated Receptor Alpha. *Critical Reviews in Toxicology;* 36:76-94.

808 Fairley KJ et al (2007) Exposure to the immunosuppressant, perfluorooctanoic acid, enhances the murine IgE and airway hyperreactivity response to ovalbumin. *Toxicological Sciences;* 97(2):375-83.

infants and young children result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.

- Multiple genes govern multiple aspects of the immune and respiratory systems, there is a great deal of heterogeneity among individuals, and variation also by gender and age. Epidemiological evidence reveals that genetic susceptibility for asthma or allergies onset can be influenced by multiple gene-environment and gene-gene interactions, as well as epigenetic mechanisms. For example, interactions between genetic and environmental factors in infants and young children result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.
- Evidence for associations between specific environmental risk factors and asthma are often inconsistent. Environmental risk factors related to asthma that are supported by considerable evidence include exposure to biological natural inhalants, childhood viral infections, ETS, other indoor and outdoor pollutants, socioeconomic status and stress, as well as to nutritional factors, gut colonization, and obesity (which influence immune system development).
- Evidence indicates heightened risk of asthma onset in children when exposure to outdoor air pollution occurs in combination with high parental stress.
- A wide range of outdoor air pollutants, such as CACs and many PAHs, acid vapours and aerosols, and diesel exhaust are associated with asthma onset and are triggers of asthma attacks.
- Indoor air pollutants may overlap with outdoor and include products of combustion such as NO2 and CO, formaldehyde, and numerous VOCs arising from consumer products such as cleaning agents, laundry, and personal care products.
- Children are exposed to complex mixtures of pollutants indoors and out, and there are enormous challenges in assessing the health impacts of many co-exposures, as well as cumulative exposures. Nevertheless, there is evidence of association between preterm birth and air pollution, which in turn affects lung development. Air pollutants also impact the immune system, some skewing it towards T_H2 cell production.
- Phthalates and BPA, well-known for their endocrine disrupting effects, have also been shown to heighten lung inflammation, and there is some evidence of immunotoxicity related to exposure to perfluorinated compounds.

14.0 Conclusions

This report was one of several activities that fulfilled a vital objective for a larger project: to learn from each other across the CPCHE and OCDPA networks and to integrate each other's knowledge about risk factors for chronic disease. Despite its length, it only scopes a vast amount of research but now provides a foundation for further detailed work including analysis of related policy issues.

It revealed a number of truths about chronic disease prevention. The perspectives and approaches to population health prevention represented by the two networks (CPCHE and OCDPA) are similar in their great complexity. There is far more complexity involved than implied when chronic disease response strategies than is implied in or amenable to response strategies focused solely on individual behavioural changes.

The challenges to be faced over the next two to three decades in addressing chronic disease are sobering given the numbers of people predicted to be affected and estimates of costs. In multiple reports, dramatic language is used to frame these predictions such as the "rising tide" of dementia, the "perfect storm of risk factors" for CVD, the epidemic of obesity and diabetes and a related "economic tsunami" of health care costs, and "no breathing room" to capture the high numbers of illness and death and very high cost of air pollution. For cancer, the hard statistics (nearly half of Canadians will get cancer and about one in four will die from it) leave no need for the dramatic language.

These predictions and this language are used against the backdrop of an aging population. Within another 20 to 30 years, one quarter of Canada's population will be senior citizens (over the age of 65). If current trends continue, over 80% of those seniors will have one or more chronic disease. This disease burden will be disproportionately felt by those live in poverty. Many severe health impacts of climate change are expected to occur in coming decades. Similarly dramatic language, equally justified, arises. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health – air, food, water and shelter.

Because of the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures explored in this report, a broader approach to prevention is worthwhile. Equally important is a critical need to address the "causes of the causes," notably poverty and the SDOH given the reality of biomedical and behavioural risk factors for various diseases arising from social and economic conditions.

Environmental influences on health are similarly multifaceted, involving multiple pollutants, exposure routes, on a scale ranging from macro to micro (e.g., from built environment features to the loading of floor dust with toxic substances), multiple interrelationships, and life course vulnerabilities. Biomonitoring data indicates population-wide exposure to multiple contaminants, with levels higher in children and generally highest in breast-fed infants, with unknown consequences.

It is already well-established that the *in utero* and perinatal "environment" and maternal and early childhood circumstances play major roles in the risk of later life disease. Within this new paradigm for disease causation, the DOHaD concept and the related field of epigenetics, a rapidly expanding body of research indicates a role for early life exposure to environmental contaminants in this lifelong continuum of disease vulnerability.

Because of the abundant complexity, not only is there a need for more research, but also to adjust assessments of the strenghth of evidence for associations between risk factors and health outcomes via tools such as the Bradford Hill criteria and hierarchical models of study designs. Given the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures, a broader approach to prevention is worthwhile. Table 1 contained in the Executive Summary to this

report provides a summary of early exposures (*in utero* or childhood) for which there is evidence of associations with prevalent chronic diseases addressed in this review. It is important to emphasize that important detail about strength of evidence (explored throughout this report) is not included in this table. Nevertheless, the multiple exposures noted indicate a priority list of substances of concern particularly those that repeat frequently across the table including air pollution (notably the CACs), lead, multiple pesticides, POPs, phthalates and BPA.

Environmental Health Institute of Canada
Institut de santé environnementale du Canada

CANADIAN ENVIRONMENTAL
LAW ASSOCIATION